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Guanylhydrazones of (Hetero)Aryl Methyl Ketones: Structure and Reaction with Acetic Anhydride[a]

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Summary. The synthesis of some novel guanylhydrazones of (hetero)aryl methyl ketones is described. Successive reaction with hot acetic anhydride leads to the corresponding N,N′-diacetyl derivatives. Structural assignments of all novel compounds and those of some already known congeners were achieved by means of NMR spectroscopic investigations (^{1}H, ^{13}C) and X-ray structure analysis.

Keywords. (Hetero)Aryl methyl ketone guanylhydrazones; Acylation; ^{1}H NMR spectroscopy; ^{13}C NMR spectroscopy; X-ray structure analysis.

Guanylhydrazone von (Hetero-)Arylmethylketonen: Struktur und Reaktion mit Acetanhydrid

Zusammenfassung. Die Synthese einiger neuer Guanylhydrazone von Aryl-bzw. Heteroarylmethylketonen wird beschrieben. Die Reaktion dieser Verbindungen mit Acetanhydrid führt zu entsprechenden N,N′-Diacetylderivaten. Die Strukturen aller neuen Verbindungen sowie die einiger bereits beschriebener Analoga wurden mit Hilfe von NMR-Untersuchungen (^{1}H, ^{13}C) sowie durch Röntgenkristallstrukturanalysen bestimmt.

Introduction

Guanylhydrazones are reaction products of oxo compounds with aminoguanidines. This class of compounds has been known for a long time [1] and is of considerable interest due to a wide variety of different biological activities found with many representatives [2, 3]. Moreover, guanylhydrazones are valuable synthetic building blocks for the construction of functionalized nitrogen-containing heterocycles [4, 5]. In this context we have recently published the transformation of aromatic

[a] Dedicated to the memory of Prof. *G. Snatzke*
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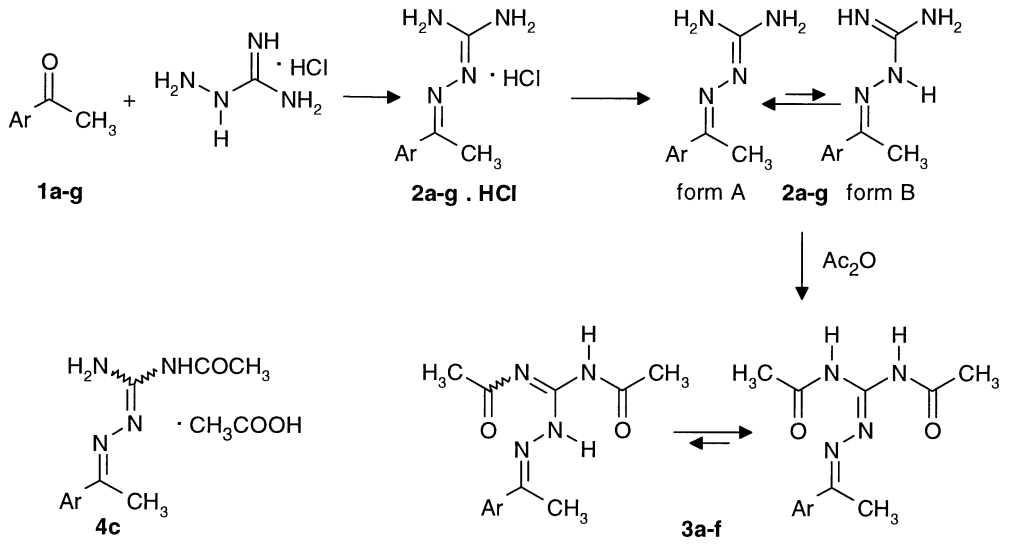
aldehyde guanylhydrazones into 3-acylamino-5-aryl-1,2-diacetyl-4,5-dihydro-1,2,4-triazoles [6], the cyclization of N^1-(glycopyranosylamino)-guanidines to 3-acetylamino-N^1-glycopyranosyl-5-methyl-1,2,4-triazoles [7], and the synthesis of N^1-cycloalkenyl substituted 3-acetylamino-5-methyl-1,2,4-triazoles from corresponding guanylhydrazones derived from cyclic ketones [8]. All these cyclizations are based on the reaction of guanylhydrazones with excessive acetic anhydride and- supposedly -proceed *via* an interesting type of ring closure mechanism [5, 6]. However, not all types of guanylhydrazones could be transformed into the corresponding 1,2,4-triazole derivatives. For instance, the reaction of camphor guanylhydrazone with acetic anhydride resulted in an N,N′-diacetylated product [8], and the same reaction behaviour was found with guanylhydrazones derived from isatin [9] or 2,6-dichlorobenzaldehyde [10]. In the light of these findings and in continuation of our previous studies on guanylhydrazones [6–10], we here report on investigations concerning guanylhydrazones derived from aryl methyl and heteroaryl methyl ketones, particularly with respect to their reaction behaviour towards acetic anhydride. Additionally, detailed NMR spectroscopic and selected X-ray structural studies of the title compounds and their reaction products are presented.

Results and Discussion

Treatment of methyl ketones **1a–g** with aminoguanidine hydrogencarbonate/HCl led to the formation of guanylhydrazones hydrochlorides **2a–g** · HCl, which were – except the pyridine derivatives – transformed into the corresponding free bases by treatment with aqueous KOH. Subsequently, the guanylhydrazones **2a–g** were reacted with an excess of acetic anhydride at 100°. Under these reaction conditions (similar to those applied in ring closure reactions described in Refs. [6–8]), in no case formation of an 1,2,4-triazole system could be observed. Spectroscopic data together with elemental analyses revealed the reaction products to be mainly the corresponding N,N′-diacetylated guanylhydrazones of type **3**. Upon reaction of the furyl derivative **2c**, a second product was isolated to which we assign structure **4c**. With the 4-pyridinyl compound **2g**, a complex mixture of reaction products was obtained which could not be separated by column chromatography. The (*Z*)-isomer of **2b** was isolated in low yield upon concentration of the mother liquor obtained from recrystallization of the crude product resulting from reaction of **1b** and aminoguanidine.

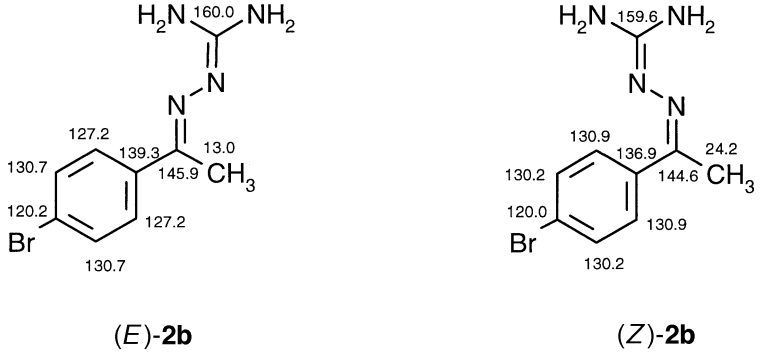
Guanylhydrazones of type **2** can exist in two tautomeric forms (A and B, Scheme 1). ^{1}H NMR spectra indicated the diaminomethylene form (A) to be present preferably in *DMSO*-d_6 solution according to two separated singlet signals of relative intensity 2 attributable to NH protons [10]. Compounds **2** can also be present in two different configurations. *i.e.* as (*E*) or (*Z*) isomers at the C=N double bond. The configuration of guanylhydrazones **2a–g** could be unambiguously deduced by comparison of the ^{13}C chemical shifts of both possible isomers in case of the bromophenyl derivative **2b** considering γ-effects. Carbon atoms in γ-position (α to C=N) to a *syn*-located hydrazone N-2 atom are upfield shifted compared to the corresponding γ-atoms in *anti*-position due to steric compression [11, 12]. Thus, the ^{13}C chemical shift ($\delta = 13.0$ ppm) of the methyl carbon atom in



Scheme 1. Ar: **a** = Ph, **b** = 4-bromophenyl, **c** = 2-furyl, **d** = 2-thienyl, **e** = 2-pyridyl, **f** = 3-pyridyl, **g** = 4-pyridyl

2b (*syn*-position of Me and the guanyl moiety) is much smaller than that of the methyl-C in the corresponding (*Z*)-isomer (*Z*)-**2b** ($\delta_{Me} = 24.2$ ppm) (Fig. 1). Reversely, the signal of Ph C-1 in (*Z*)-**2b** ($\delta = 136.9$ ppm) is characterized by a 2.4 ppm upfield shift compared to that of Ph C-1 in (*E*)-configured **2b** ($\delta = 139.3$ ppm). Thus, considering the ^{13}C chemical shifts of the methyl carbons in guanylhydrazones **2a**–**g** (located within 13.0–14.5 ppm), these compounds can be assigned (*E*)-isomers, as well as their N,N′-diacetyl congeners of type **3** ($\delta_{Me} = 13.7$–14.9 ppm) and the monoacetyl compound **4c** ($\delta_{Me} = 13.4$ ppm). This conclusion was fully confirmed by X-ray crystal structure analyses of selected compounds.

An interesting phenomenon was observed when studying NOE effects with compounds of type **3**. In NOE difference experiments, irradiation of one (of the two non-equivalent) $COCH_3$ transitions enhances both NH signals to the same extent (what still could be explained by NH proton exchange), but also massive



(*E*)-**2b** (*Z*)-**2b**

Fig. 1. ^{13}C Chemical shifts (δ, ppm) of the (*E*)- and (*Z*)-isomer of guanylhydrazone **2b**

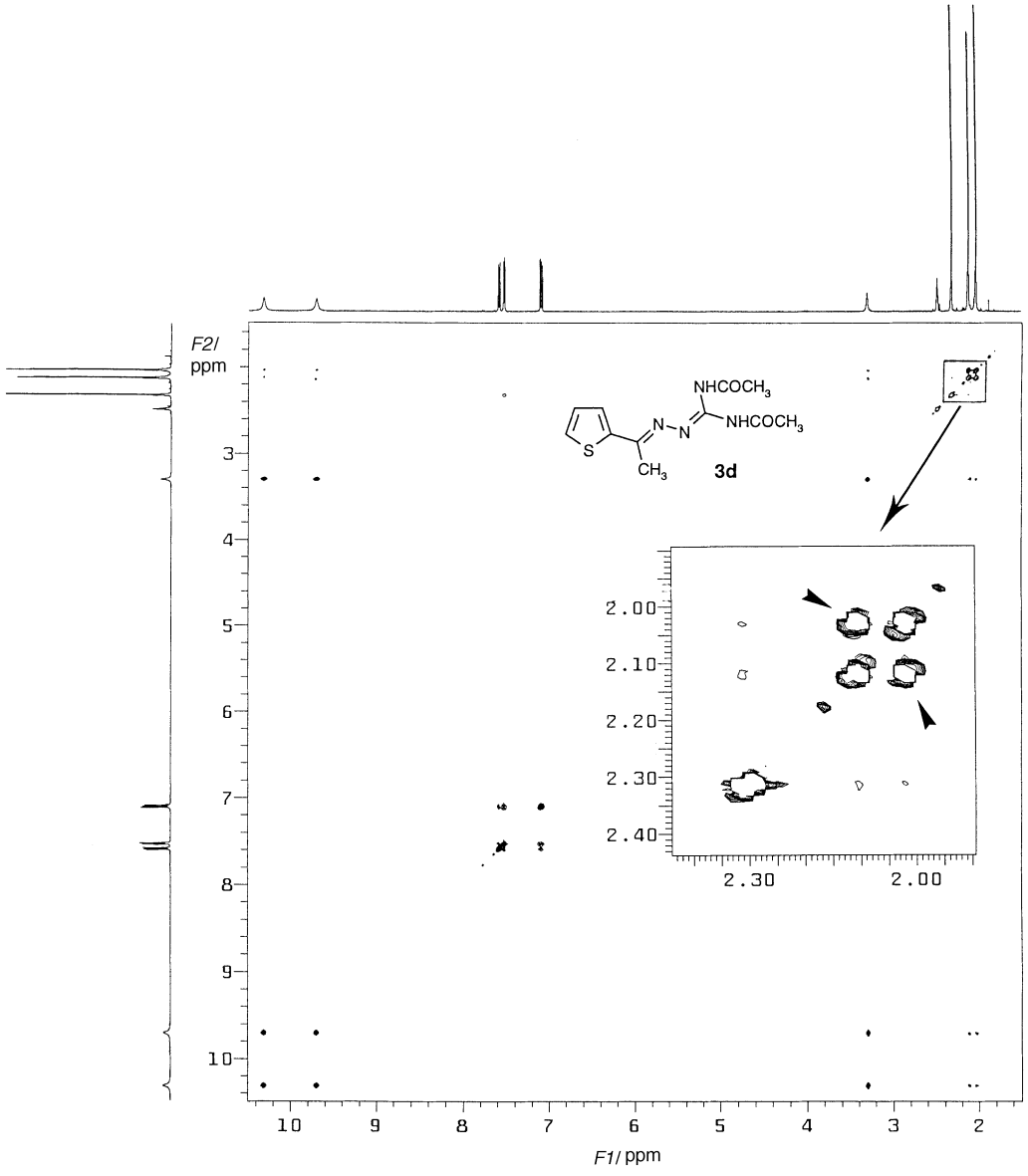
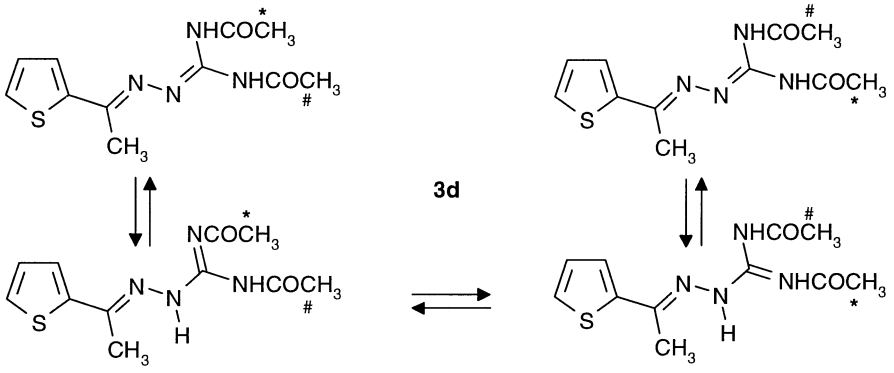


Fig. 2. Phase-sensitive NOESY spectrum of **3d**

saturation transfer to the other $COCH_3$ signal was observed. Too high irradiation power as the reason for the latter finding could be excluded as a step-by-step decrease of power by overall 10 dB did not result in any change. Also, phase-sensitive NOESY spectra, which permit to distinguish between cross peaks due to chemical exchange from these resulting from positive NOEs on basis of their phase properties [13] show the same phenomenon. Accordingly, in the NOESY spectrum of **3d** strong, positive cross peaks (indicated with arrowheads in Fig. 2) correlate the two signals of $COCH_3$, indicating a chemical exchange process, whereas small negative ones reflect NOEs between each $COCH_3$ group and the N=C–CH_3 protons (Fig. 2).



Scheme 2

A possible explanation of these observations might be an equilibrium process (slow compared to the NMR timescale) as indicated in Scheme 2. This is supported by the fact that the signals of the $COCH_3$ protons (as well as those of NH) show a temperature dependence leading to coalescence at approximately 150°C in *DMSO*-d_6.

The ^1H and ^{13}C NMR data of compounds investigated are given in the Experimental section. Assignments for all proton and carbon resonances are based on ^1H-coupled ^{13}C NMR spectra (gated decoupling), APT [14], 1D-HETCOR [15], and long-range INEPT experiments [16] with selective excitation as well as on NOE difference experiments [13] and HMQC spectra [17]. The two acetyl moieties in compounds **3** could not be assigned unambiguously.

Crystal structures of **2c**, **2d**, **3b**, **3d**, *and* **3f**

Crystal structure determinations by X-ray diffraction were attempted on two guanylhydrazones and six diacetyl derivatives. Due to crystal quality and size problems, only five compounds could be studied. Technical details on the structure determinations are given in the Experimental section and in Table 1. Views of the molecules including hydrogen bonds are shown in Figs. 3 to 7, and selected geometric data of the compounds are presented in Table 2.

The structure analyses proved all five investigated compounds to adopt the A-type tautomer (Scheme 1) and (*E*)-configuration. The two guanylhydrazones **2c** and **2d** and the diacetyl compounds **3b** and **3d** are in the crystalline state flat but not perfectly planar. Disregarding hydrogen atoms, the r.m.s deviations from planarity are 0.113, 0.228, 0.095, and 0.200 Å. In **2c** and **2d**, the guanidine moieties C(1)–N(1)–N(2)–N(3) are inclined by about 11° and 29° against the rest of the molecule. **2d** contains in the crystalline state about 12% of a rotamer in which the thiophene ring is rotated by 180° about the C(6)–C(8) bond compared to Fig. 4, resulting in a *syn*-orientation of the thiophene S atom to the methyl group. In the furyl compound **2c** such a feature was not observed, whereas in the diacetyl thiophene compound **3d** about 5% of the thiophene rings adopt the corresponding orientation. A conformation largely different from **3b** and **3d** is found in the diacetyl-pyridinyl compound **3f**. Here, the two acetyl oxygen atoms are in principle

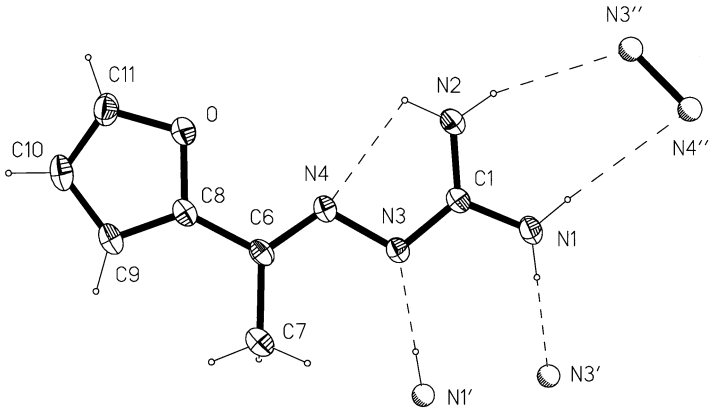


Fig. 3. Molecular structure of **2c** in the crystalline state (20% probability ellipsoids) with hydrogen bonds including those to neighbouring molecules

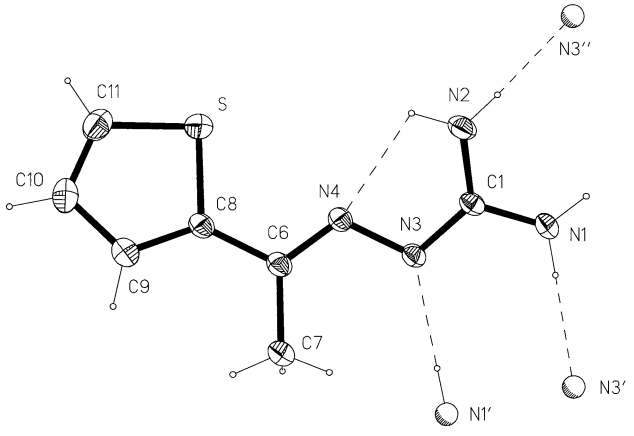


Fig. 4. Molecular structure of **2d** in the crystalline state with hydrogen bonds including those to neighbouring molecules

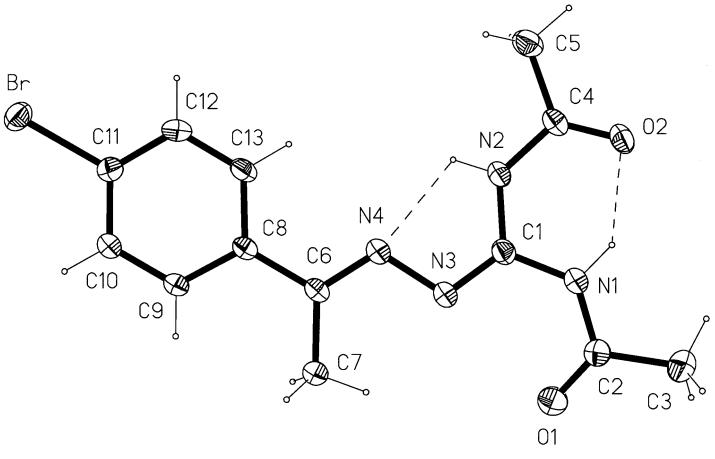


Fig. 5. Molecular structure of **3b** in the crystalline state with hydrogen bonds

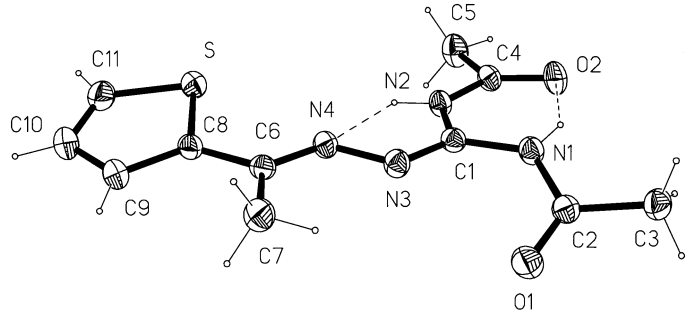


Fig. 6. Molecular structure of **3d** in the crystalline state with hydrogen bonds

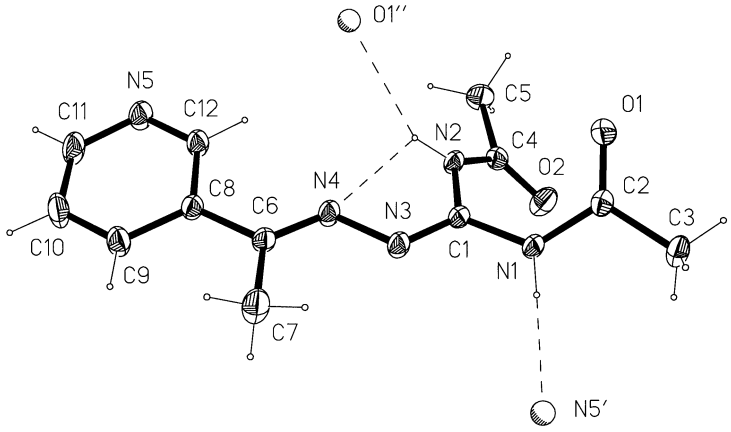


Fig. 7. Molecular structure of **3f** in the crystalline state with hydrogen bonds including those to neighbouring molecules

syn-oriented, and due to sterical hinderance both acetyl functions are distinctly turned out from the plane through the rest of the molecule (Fig. 7), the angles to this least-squares plane being 35° for N(1)–(C(2)=O(1))–C(3) and 41° for N(2)–(C(4)=O(2))–C(5).

The bond length patterns of the guanidine moieties of the five compounds are similar (Table 2). Bond lengths and angles in the aryl moieties, not given in Table 2, correspond with literature data. All nitrogen atoms show essentially planar coordinations and can therefore be considered as sp^2-hybridized. In the guanylhydrazones **2c** and **2d**, the C(1)–N bond lengths to the two terminal amino nitrogen atoms are only by 0.02 Å longer than to the hydrazine nitrogen N(3), indicating that the three C(1)–N-bonds exhibit bond orders close to 1.33 valence units. In the three diacetyl compounds **3b**, **3d**, and **3f** the C(1)–N(1),N(2) bond distances to the amino nitrogen atoms are by about 0.05 Å longer than before, whereas the C(1)–N(3) bond to the hydrazine nitrogen is shorter by 0.03 Å. Thus, the three C(1)–N bonds approach a single/single/double bond pattern but retain nonetheless for C(1)–N(1) and C(1)–N(2) some multiple bond character. The other bonds in the central part of the molecules exhibit essentially agreeing characteristics for both the guanyl hydrazones **2c** and **2d** as well as for the diacetyl compounds **3b**,

Table 1. Crystallographic data for **2c**, **2d**, **3b**, **3d**, and **3f**

	2c	**2d**	**3b**	**3d**	**3f**
Formula	$C_7H_{10}N_4O$	$C_7H_{10}N_4S$	$C_{13}H_{15}BrN_4O_2$	$C_{11}H_{14}N_4O_2S$	$C_{12}H_{15}H_5O_2$
Fw	166.19	182.25	339.20	266.32	261.29
Cryst. size (mm)	0.45×0.18×0.10	0.52×0.45×0.42	0.45×0.24×0.18	0.50×0.42×0	0.50×0.35×0.22
Crystal system	monoclinic	monoclinic	monoclinic	orthorhombic	monoclinic
Space group	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	*P*bca (No. 61)	$P2_1/n$ (No. 14)
a(Å)	11.028(6)	15.189(4)	8.997(3)	7.013(2)	11.877(4)
b(Å)	7.473(4)	7.432(2)	21.830(8)	18.485(4)	7.373(3)
c(Å)	10.887(6)	8.234(2)	7.890(3)	20.401(4)	15.120(5)
β(deg)	108.00(1)	103.15(1)	105.77(2)		96.79(1)
V(Å^3)	853.3(8)	905.1(4)	1491.3(9)	2644.7(11)	1314.8(8)
Z	4	4	4	8	4
ρ_{calc},(g · cm^{-3})	1.294	1.337	1.511	1.338	1.320
T(K)	298	298	299	299	299
μ(mm^{-1})	0.093	0.308	2.763	0.245	0.094
θ_{max}(deg)	25	27	27	27	27
Index ranges	$-12 \le h \le 13$	$-19 \le h \le 19$	$-11 \le h \le 11$	$-8 \le h \le 8$	$-15 \le h \le 15$
	$-8 \le k \le 8$	$-9 \le k \le 9$	$-27 \le k \le 27$	$-23 \le k \le 23$	$-9 \le k \le 9$
	$-12 \le l \le 12$	$-10 \le l \le 10$	$-10 \le l \le 10$	$-24 \le l \le 26$	$-19 \le l \le 19$
No. of rflns measd.	9038	11172	18929	26629	16235
No. of unique rflns	1493	1966	3249	2868	2843
No. of rflns $I > 2\sigma(I)$	1115	1677	2380	2357	2312
No. of params.	124	140	198	177	185
$R(F)(I > 2\sigma(I))$	0.037	0.031	0.031	0.033	0.036
R(F) (all data)	0.056	0.037	0.053	0.042	0.046
$wR(F2)$ (all data)	0.106	0.092	0.067	0.090	0.105
Diff. *Fourier* peaks (min/max) (e · Å^3)	−0.14/0.17	−0.14/0.15	−0.18/0.27	−0.13/0.20	−0.15/0.19

3d, and **3f**. The bond N(3)–N(4) (mean value 1.403 Å) is essentially a single bond, N(4)–C(5) (mean value 1.288 Å) approaches a double bond, and C(5)–C(8) (mean value 1.467 Å) – the formal signal bond to the aryl residue – exhibits some conjugation effect. Noteworthy, the bond angles around C(1) exhibit consistently high values of about 124° for N(2)–C(1)–N(3) (cf. Table 2), indicating the presence of a repulsion effect, possibly between N(2) and the lone pair of N(4).

An integral part of all five compounds are their hydrogen bonds. Persistent for all five compounds is the strongly bent intramolecular hydrogen bond N(2)–H···N(4) with mean dimensions of N(2)–H = 0.86 Å, N(2)···N(4) = 2.57 Å, H···N(4) = 2.19 Å, and N(2)–H···N(4) = 107° (cf. Figs. 3 to 7 and Table 2). Another intramolecular and distinctly bent hydrogen bond N(1)–H···O(2) with mean dimensions N···O = 2.68 Å, H···O = 1.94 Å, and N–H···O = 140° contributes to the stability of the two diacetyl compounds **3b** and **3d**. This bond is missing in the diacetyl pyridinyl compound **3f**, where, due to the aberrant relative orientation of the aminoacetyl group N(1)–(C(2)=O(1))–C(3), it is replaced by an almost linear intermolecular hydrogen bond N(1)–H···N(5′) with the pyridine nitrogen of a neighbouring molecule as acceptor. Since in this compound the second

Table 2. Selected bond lengths and angles for **2c**, **2d**, **3b**, **3d**, and **3f**

	2c	**2d**	**3b**	**3d**	**3f**	Mean values[1]
C(1)–N(1)	1.343(2)	1.342(2)	1.378(3)	1.385(2)	1.393(2)	1.343/1.385
C(1)–N(2)	1.334(2)	1.353(2)	1.389(3)	1.389(2)	1.387(2)	1.343/1.388
C(1)–N(3)	1.323(2)	1.321(2)	1.291(2)	1.292(3)	1.293(2)	1.322/1.292
N(3)–N(4)	1.406(2)	1.391(2)	1.412(2)	1.402(2)	1.403(2)	1.403
N(1)–C(2)			1.370(3)	1.372(2)	1.372(2)	1.371
N(2)–C(4)			1.367(3)	1.370(2)	1.380(2)	1.372
C(2)–O(1)			1.206(3)	1.209(2)	1.218(2)	1.211
C(4)–O(2)			1.222(2)	1.218(2)	1.208(2)	1.216
C(2)–C(3)			1.496(3)	1.501(2)	1.500(2)	1.499
C(4)–C(5)			1.495(3)	1.492(2)	1.501(2)	1.496
N(4)–C(6)	1.294(2)	1.285(2)	1.289(2)	1.291(2)	1.279(2)	1.288
C(6)–C(7)	1.498(2)	1.496(2)	1.502(3)	1.497(2)	1.504(2)	1.499
C(6)–C(8)	1.452(2)	1.457(2)	1.484(3)	1.457(2)	1.485(2)	1.467
N(1)–C(1)–N(2)	118.1(2)	117.1(1)	115.4(2)	115.6(1)	118.5(1)	116.9
N(1)–C(1)–N(3)	117.4(2)	118.3(1)	121.7(2)	121.6(1)	117.2(1)	119.2
N(2)–C(1)–N(3)	124.5(2)	124.6(1)	122.9(2)	122.8(1)	124.3(1)	123.8
C(1)–N(3)–N(4)	110.3(1)	109.9(1)	110.7(2)	110.7(1)	111.2(1)	110.6
N(3)–N(4)–C(6)	115.8(1)	117.2(1)	114.2(2)	114.4(1)	115.2(1)	115.4
N(1)···A[2]	3.047 N(3′)	3.077 N(3′)	2.674 O(2)	2.678 O(2)	2.947 N(5′)	
N(1)···A	3.295 N(4″)	[3.459 N(2″)]				
N(2)···A	2.579 N(4)	2.578 N(4)	2.551 N(4)	2.545 N(4)	2.589 N(4)[3]	
N(2)···A	3.195 N(3″)	3.228 N (3‴)				

[1] First three lines give separate mean values for (**2c**, **2d**), and for (**3b**, **3d**, and **3f**); [2] hydrogen bond distances and acceptor atoms; unprimed acceptors for intramolecular, primed acceptors for intermolecular hydrogen bonds; [3] bifurcated hydrogen bond with second branch N(2)···O(1′) = 3.126 Å

aminoacetyl group shows an aberrant orientation as well, the intramolecular hydrogen bond N(2)–H···N(4) is supplemented by a bifurcated intermolecular interaction with O(1″) as the second acceptor. The guanyl hydrazones **2c** and **2d** have three further H atoms for hydrogen bonding. Both compounds, although not being isostructural, agree in forming an H-bonded dimer *via* the bond N(1)–H···N(3′) and a centre of inversion. In **2c**, the remaining two hydrogen atoms are directed to N(3″) and N(4″) of another symmetry equivalent molecule which with its mean plane is oriented roughly along the view direction of Fig. 3 corresponding to interactions between H atoms and the π-electrons of the hydrazine moiety. A related situation is present in **2d** for N(2)–H···N(3″), whereas the second hydrogen atom of N(1) is directed to the amino nitrogen of a neighbouring molecule with N(1)···N(2‴) = 3.46 Å.

Experimental

Melting points were determined on a Boëtius hot-stage microscope and are uncorrected. MS spectra were obtained on a Shimadzu QP 1000 spectrometer (EI, 70 eV). All NMR spectra were recorded on a Varian Unity*plus* 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) from *DMSO*-d_6

solutions at 28°C. The solvent signal was used as an internal standard which was related to *TMS* with $\delta = 2.49$ ppm (^{1}H) and $\delta = 39.5$ ppm (^{13}C). The digital resolutions were 0.25 Hz/data point for the ^{1}H NMR spectra, 0.56 Hz/data point for the broad-band decoupled ^{13}C NMR spectra, and 0.33 Hz/data point for the gated decoupled ^{13}C NMR spectra. The results of elemental analyses for the new compounds agreed satisfactorily with the calculated ones.

General procedure for the preparation of guanylhydrazones **2a–d**

Aminoguanidine hydrogencarbonate (2.72 g, 20 mmol) was dissolved in 10 cm^3 of 2 *N* HCl. After vigorous evolution of CO_2 had ceased, 20 mmol of ketone **1a–e** was added and the mixture was treated as described below.

2-((E)-1-Phenylethylidine)-1-hydrazinecarboximidamide ((*E*)-**2a**)

The reaction mixture was stirred at room temperature. After a few minutes, **2a** · HCl separated quantitatively from the solution to afford crystals of m.p. 202–203°C (Ref. [18]: m.p.: 202–203°C). The salt **2a** · HCl (4.28 g, 20 mmol) was dissolved in 200 cm^3 of hot water and treated with excessive 2 *N* KOH. The precipitated free base (3.36 g, 95%) was recrystallized from hot water to give 2.74 g (78%) of shiny plates of m.p. 183–184°C (Ref. [19]: m.p.: 182–184°C).

MS: $m/z = 176$ (M^+, 51%), 175 (54), 161 (33), 133 (57), 104 (52), 103 (53), 78 (68), 77 (100), 63 (21), 58 (86), 51 (85), 45 (27); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.22 (s, 3H, CH_3), 5.47 (s, 2H, NH_2), 5.84 (s, 2H, NH_2), 7.23 (m, 1H, Ph H-4), 7.31 (m, 2H, Ph H-3,5), 7.78 (m, 2H, Ph H-2,6) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 13.3 (CH_3, $^1J(CH_3) = 127.2$ Hz), 125.3 (Ph C-2,6), 127.1 (Ph C-4), 127.9 (Ph C-3,5), 140.1 (Ph C-1), 147.1 (ArC=N), 159.7 (N=C–N) ppm.

2-((E)-1-(4-Bromophenyl)ethylidene)-1-hydrazinecarboximidamide ((*E*)-**2b**; $C_9H_{11}BrN_4$) and *2-((Z)-1-(4-Bromophenyl)ethylidene)-1-hydrazinecarboximidamide* ((*Z*)-**2b**; $C_9H_{11}BrN_4$)

The ketone was added dissolved in 20 cm^3 of MeOH and the reaction mixture was then heated to reflux for 1 h. After cooling, the separated crystals of **2b** · HCl were collected (5.71 g, 98%). The free base was obtained as described for **2a**. Yield: 88% of (*E*)-**2b**, m.p.: 189–190°C. An analytical sample was recrystallized from hot water to afford colorless crystals of m.p. 193–196°C.

MS: $m/z = 256/254$ (M^+, 24%/27%), 255/253 (23/22), 241/239 (21/19), 213/211 (24/24), 184/182 (22/22), 103 (63), 102 (44), 99 (24), 79 (20), 78 (22), 77 (93), 76 (47), 75 (51), 74 (26), 73 (29), 72 (39), 66 (23), 65 (21), 58 (100), 55 (21), 52 (28), 51 (78), 50 (73), 45 (36); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.19 (s, 3H, CH_3), 5.54 (s, 2H, NH_2), 5.89 (s, 2H, NH_2), 7.46 (m, 2H, Ph H-3,5), 7.73 (m, 2H, Ph H-2,6) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 13.0 (CH_3, $^1J(CH_3) = 127.4$ Hz), 120.2 (Ph C-4), 127.2 (Ph C-2,6), 130.7 (Ph C-3,5), 139.3 (Ph C-1), 145.9 (ArC=N), 160.0 (N=C–N) ppm.

The mother liquor obtained upon recrystallization of crude **2b** was concentrated leading to separation of colorless crystals of (*Z*)-**2b**.

Yield: 3%; m.p.: 122–124°C; ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.16 (s, 3H, CH_3), 5.21 (s, 2H, NH_2), 5.71 (s, 2H, NH_2), 7.49 (m, 2H, Ph H-3,5), 7.67 (m, 2H, Ph H-2,6) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 24.2 (CH_3, $^1J(CH_3) = 126.7$ Hz), 120.0 (Ph, C-4), 130.2 (Ph C-3,5), 130.9 (Ph C-2,6), 136.9 (Ph C-1), 144.6 (ArC=N), 159.6 (N=C–N) ppm.

2-((E)-1-(2-Furyl)ethylidene)1-hydrazinecarboximidamide ((*E*)-**2c**; $C_7H_{10}N_4O$)

The reaction mixture was heated to 90–95°C for 20 min. The cooled solution was treated with excessive 2 *N* KOH and then evaporated *in vacuo* until separation of crystals began.

Yield: 59% of deep yellow crystals; m.p.: 159–160°C; MS: $m/z = 166$ (M^+, 38%), 151 (35), 94 (32), 66 (100), 65 (44), 58 (26); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.11 (s, 3H, CH_3), 5.57 (s, 2H, NH_2), 5.78 (s, 2H, NH_2), 6.47 (dd, ^3J(H3, H4) = 3.4 Hz, ^3J(H4, H5) = 1.8 Hz, 1H, furane H-4), 6.65 (dd, ^3J(H3, H4) = 3.4 Hz, ^4J(H3, H5) = 0.7 Hz, furane H-3), 7.59 (dd, ^3J(H4, H5) = 1.8 Hz, ^4J(H3, H5) = 0.7 Hz, 1H, furane H-5) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 13.2 (CH_3, $^1J(CH_3)$ = 128.0 Hz), 106.4 (furane C-3, ^1J(C3, H3) = 175.7 Hz, ^2J(C3, H4) = 4.0 Hz, ^3J(C3, H5) = 5.8 Hz), 111.4 (furane C-4, ^1J(C4, H4) = 174.7 Hz, ^2J(C4, H3) = 4.0 Hz, ^2J(C4, H5) = 13.3 Hz), 140.4 (ArC = N, ^2J(C=N, CH_3) = 6.4 Hz), 142.1 (furane C-5, ^1J(C5, H5) = 203.4 Hz, ^2J(C5, H4) = 10.8 Hz, ^3J(C5, H3) = 7.5 Hz), 154.4 (furane C-2), 159.6 (N=C–N) ppm.

2-((E)-1-(2-Thienyl)ethylidene)-1-hydrazinecarboximidamide ((*E*)-**2d**; $C_7H_{10}N_4S$)

The reaction mixture was stirred for 16 h. Addition of excessive 2 *N* KOH precipitated the oily free base which solidified on scratching (95% yield). Recrystallization from EtOH afforded 55% of cream colored crystals with m.p. 137–139°C (Ref. [20]: m.p.: 83–83.5°C).

MS: $m/z = 182$ (M^+, 76%), 167 (71), 110 (89), 109 (45), 104 (25), 103 (34), 99 (22), 84 (26), 78 (22), 77 (54), 76 (28), 73 (21), 72 (22), 69 (32), 66 (58), 65 (39), 58 (100), 57 (31), 56 (26), 55 (21), 52 (24), 51 (63), 50 (47); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.19 (s, 3H, CH_3), 5.58 (s, 2H, NH_2), 5.70 (s, 2H, NH_2), 6.98 (dd, ^3J(H3, H4) = 3.7 Hz, ^3J(H4, H5) = 5.1 Hz, 1H, Th H-4), 7.15 (dd, ^3J(H3, H4) = 3.7 Hz, ^4J(H3, H5) = 1.1 Hz, Th H-3), 7.29 (dd, ^3J(H4, H5) = 5.1 Hz, ^4J(H3, H5) = 1.1 Hz, 1H, Th H-5) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 13.9 (CH_3, $^1J(CH_3)$ = 127.9 Hz), 123.6 (Th C-3, ^1J(C3, H3) = 166.2 Hz), 125.2 (Th C-5), 127.1 (Th C-4, ^1J(C4, H4) = 166.7 Hz), 144.1 (ArC=N), 146.7 (Th C-2), 159.3 (N=C–N) ppm.

2-((E)-1-(2-Pyridyl)ethylidene)-1-hydrazinecarboximidamide dihydrochloride
((*E*)-**2e** · 2HCl; $C_8H_{13}Cl_2N_5$)

Aminoguanidine hydrogencarbonate (2.72 g, 20 mmol) was dissolved in 20 cm^3 of 2 *N* HCl. After addition of 2-acetylpyridine (2.42 g, 20 mmol) the reaction mixture was heated to reflux for 1 h. Then the water was evaporated *in vacuo*, the residue was treated with MeOH, and the salt **2e** · 2HCl was filtered off and washed with MeOH.

Yield: 57% of nearly colorless crystals; m.p.: 240°C (decomp.); MS: $m/z = 177$ (M^+-2HCl, 26%), 162 (52), 134 (31), 106 (45), 105 (27), 104 (42), 99 (60), 79 (55), 78 (100), 73 (23), 58 (54), 52 (53), 51 (81), 50 (36); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.48 (s, 3H, CH_3), 5.20 (broad s, 4H, NH_2), 7.94 (m, 1H, Py H-5), 8.28 (broad s, 1H, NH), 8.42 (m, 1H, Py H-3), 8.51 (m, 1H, Py H-4), 8.82 (m, 1H, Py H-6), 12.10 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 13.6 (CH_3, $^1J(CH_3)$ = 129.9 Hz), 124.5 (Py C-3), 126.5 (Py C-5), 143.9 (Py C-4), 144.8 (Py C-6), 145.0 (Py C-2), 147.7 (ArC=N), 156.2 (N=C–N) ppm.

2-((E)-1-(3-Pyridyl)ethylidene)-1-hydrazinecarboximidamide hydrochloride
((*E*)-**2f** · HCl; $C_8H_{12}ClN_5$) [21]

Prepared similarly as described for **2e** · 2HCl; yield: 75% of a colorless powder; m.p.: 226–233°C (decomp.); MS: $m/z = 177$ (M^+-HCl, 16%), 176 (100), 134 (85), 105 (22), 104 (34), 79 (22), 78 (54), 77 (33), 58 (43), 52 (52), 51 (84), 50 (45); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.41 (s, 3H, CH_3), 7.68 (m, 1H, Py H-5), 8.06 (s, 4H, NH_2), 8.61 (m, 1H, Py H-4), 8.69 (m, 1H, Py H-6), 9.29 (m, 1H, Py H-2), 11.69 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 14.5 (CH_3, $^1J(CH_3)$ = 128.9 Hz), 124.6 (Py C-5), 133.8 (Py C-3), 137.3 (Py C-4), 144.9 (Py C-2), 146.8 (Py C-6), 148.4 (ArC=N), 156.3 (N=C–N) ppm.

2-((E)-1-(4-Pyridyl)ethylidene)-1-hydrazinecarboximidamide ((*E*)-**2g** · HCl; $C_8H_{12}ClN_5$)

Prepared similarly as described for **2e** · HCl; yield: 85% of a yellowish crystals; m.p.: 286–292°C); MS: $m/z = 177$ (M^+-HCl, 50%), 176 (64), 134 (48), 106 (22), 105 (23), 104 (28), 79 (23), 78 (60), 77 (34), 58 (79), 52 (52), 51 (100), 50 (49); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.36 (s, 3H, CH_3), 7.92 (m, 2H, Py H-3,5), 7.99 (s, 4H, NH_2), 8.62 (m, 2H, Py H-2,6), 11.57 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 14.1 (CH_3, $^1J(CH_3) = 128.9$ Hz), 120.7 (Py C-3,5), 143.9 (Py C-4), 149.4 (ArC=N), 149.7 (Py C-2,6), 156.2 (N=C–N) ppm.

General procedure for the reaction of guanylhydrazones **2** *with acetic anhydride*

The guanylhydrazones (5 mmol) was suspended in 7 cm^3 of acetic anhydride and the mixture was stirred at 100°C for 1 h. Then the mixture was evaporated *in vacuo*, and the semicrystalline residue was 2–3 times codistilled with toluene to remove volatile components. The residue was then recrystallized from the appropriate solvent given below.

(E)-N,N′-2-((1-Phenylethylidene)carbohydrazonoyl)bis-(acetamide) ((*E*)-**3a**; $C_{13}H_{16}N_4O_2$)

Yield: 82% of nearly colorless crystals; m.p.: 113–114°C (toluene); MS: $m/z = 260$ (M^+, 5%), 217 (43), 203 (100), 202 (37), 201 (74), 186 (21), 175 (36), 161 (73), 160 (25), 159 (98), 141 (28), 133 (58), 118 (23), 104 (54), 103 (46), 99 (22), 78 (30), 77 (46); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.09 (s, 3H, $COCH_3$), 2.18 (s, 3H, $COCH_3$), 2.36 (s, 3H, CH_3), 7.42 (m, 3H, Ph H-3,4,5), 7.93 (m, 2H, Ph H-2,6), 9.90 (s, 1H, NH), 10.39 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 14.9 (CH_3, $^1J(CH_3) = 128.3$ Hz), 24.0 ($COCH_3$, $^1J(CH_3) = 128.9$ Hz), 24.7 ($COCH_3$, $^1J(CH_3) = 128.9$ Hz), 126.8 (Ph C-2,6), 128.2 (Ph C-3,5), 129.6 (Ph C-4), 138.0 (Ph C-1), 143.8 (N=C–N), 160.7 (ArC=N), 169.6 ($COCH_3$), 169.8 ($COCH_3$) ppm.

(E)-N,N′-(2-(1-(4-Bromophenyl)ethylidene)carbohydrazonoyl)bis-(acetamide)
((*E*)-**3b**; $C_{13}H_{15}BrN_4O_2$)

Yield: 53% of yellowish crystals; m.p.: 134–137°C (EtOH); MS: $m/z = 340/338$ (M^+, 5%/5%), 298/296 (32/32), 297 (27), 295 (23), 283 (76), 281 (100), 279 (28), 255 (20), 241 (46), 239 (95), 237 (49), 211 (23), 181 (21), 141 (22), 103 (34), 102 (37), 77 (33); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.09 (s, 3H, $COCH_3$), 2.17 (s, 3H, $COCH_3$), 2.33 (s, 3H, CH_3), 7.60 (m, 2H, Ph H-3,5), 7.89 (m, 2H, Ph H-2,6), 9.92 (s, 1H, NH), 10.41 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 14.7 (CH_3, $^1J(CH_3) = 128.5$ Hz), 24.0 ($COCH_3$, $^1J(CH_3) = 128.9$ Hz), 24.7 ($COCH_3$, $^1J(CH_3) = 128.9$ Hz), 123.1 (Ph C-4), 128.8 Ph C-2,6), 131.1 (Ph C-3,5), 137.2 (Ph C-1), 144.0 (N=C–N), 159.7 (ArC=N), 169.6 ($COCH_3$), 169.8 ($COCH_3$) ppm.

(E)-N,N′-(2-(1-(2-Furyl)ethylidene)carbohydrazonoyl)bis-(acetamide) ((*E*)-**3c**; $C_{11}H_{14}N_4O_3$)

Yield: 61% of yellow crystals; m.p.: 135–137°C (EtOH); MS: $m/z = 250$ (M^+, 30%), 208 (55), 193 (68), 151 (69), 149 (32), 124 (30), 95 (27), 94 (69), 93 (20), 66 (100), 65 (55); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.08 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$), 2.24 (s, 3H, CH_3), 6.61 (dd, ^3J(H3, H4) = 3.4 Hz, ^3J(H3, H5) = 1.7 Hz, 1H, furane H-4), 7.09 (dd, ^3J(H3, H4) = 3.4 Hz, ^4J(H3, H5) = 0.7 Hz, furane H-3), 7.81 (dd, ^3J(H4, H5) = 1.7 Hz, ^4J(H3, H5) = 0.7 Hz, 1H, furane H-5), 9.83 (s, 1H, NH), 10.38 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 14.2 (CH_3, $^1J(CH_3) = 129.2$ Hz), 24.0 ($COCH_3$, $^1J(CH_3) = 128.9$ Hz), 24.7 ($COCH_3$, $^1J(CH_3) = 128.9$ Hz), 111.8 (furane C-3, ^1J(C3, H3) = 177.0 Hz, ^2J(C3, H4) = 4.3 Hz, ^3J(C3, H5) = 5.7 Hz), 112.0 (furane C-4, ^1J(C4, H4) = 176.3 Hz), ^2J(C4, H3) = 4.0 Hz, ^2J(C4, H5) = 13.3 Hz), 143.8 (N=C–N), 144.6 (furane

C-5, ^1J(C5, H5) = 204.7 Hz, ^2J(C5, H4) = 10.9 Hz, ^3J(C5, H3) = 7.7 Hz), 152.3 (furane C-2), 152.4 (ArC=N), ^2J(C=N,CH_3) = 6.6 Hz), 169.6 (*C*OCH_3, ^2J(CO, CH_3) = 6.5 Hz), 169.8 (*C*OCH_3, ^2J(CO, CH_3) = 6.5 Hz) ppm.

(E)-N,N′-(2-(1-(2-Thienyl)ethylidene)carbohydrazonoyl)bis-(acetamide) ((*E*)-**3d**; $C_{11}H_{14}N_4O_2S$)

Yield: 75% of yellowish crystals; m.p.: 129–130°C (EtOH); MS: *m/z* = 266 (M^+, 29%), 224 (59), 209 (66), 167 (74), 165 (24), 140 (22), 110 (100), 99 (24), 98 (22), 69 (47), 66 (51), 58 (34), 45 (51); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.05 (s, 3H, $COCH_3$), 2.14 (s, 3H, $COCH_3$), 2.33 (s, 3H, CH_3), 7.10 (dd, ^3J(H3, H4) = 3.7 Hz, ^3J(H4, H5) = 5.1 Hz, 1H, Th H-4), 7.53 (dd, ^3J(H3, H4) = 3.7 Hz, ^4J(H3, H5) = 1.2 Hz, Th H-3), 7.59 (dd, ^3J(H4, H5) = 5.1 Hz, ^4J(H3, H5) = 1.2 Hz, 1H, Th H-5), 9.71 (s, 1H, NH), 10.33 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 15.1 (CH_3, ^1J(CH_3) = 129.0 Hz), 23.8 (CO*C*H_3), ^1J(CH_3) = 128.9 Hz), 24.5 (CO*C*H_3, ^1J(CH_3) = 128.9 Hz), 127.5 (Th C-4, ^1J(C4, H4) = 168.6 Hz), 128.1 (Th C-3, ^1J(C3, H3) = 167.5 Hz, ^2J(C3, H4) = 5.9 Hz, ^3J(C3,H5) = 9.2 Hz), 128.9 (Th C-5, ^1J(C5, H5) = 186.5 Hz, ^2J(C5, H4) = 7.2 Hz, ^3J(C5, H3) = 10.5 Hz), 143.4 (N=C=N), 143.6 (Th C-2), 156.3 (ArC=N), 169.2 (*C*OCH_3), 169.5 (*C*OCH_3) ppm.

(E)-N,N′(2-(1-(2-Pyridyl)ethylidene)carbohydrazonoyl)bis-(acetamide) ((*E*)-**3e**; $C_{12}H_{15}N_5O_2$)

Yield: 38% of colorless crystals; m.p.: 176–177°C (EtOH); MS: *m/z* = 261 (M^+,1%), 204 (42), 183 (32), 141 (70), 134 (24), 106 (64), 104 (31), 99 (37), 98 (49), 79 (56), 78 (100), 52 (39), 51 (56); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.10 (s, 3H, $COCH_3$), 2.19 (s, 3H, $COCH_3$), 2.40 (s, 3H, CH_3), 7.41 (m, 1H, Py H-5), 7.83 (m, 1H, Py H-4), 8.31 (m, 1H, Py H-3), 8.61 (m, 1H, Py, H-6), 9.96 (s, 1H, NH), 10.46 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 13.7 (CH_3, ^1J(CH_3) = 128.9 Hz), 24.0 (CO*C*H_3), 24.7 (CO*C*H_3), 121.2 (Py C-3), 124.3 (Py C-5), 136.2 (Py C-4), 144.3 (N=C–N), 148.5 (Py C-6), 155.4 (Py C-2), 161.8 (ArC=N), 169.7 (*C*OCH_3), 169.8 (*C*OCH_3) ppm.

(E)-N,N′-(2-(1-(3-Pyridyl)ethylidene)carbohydrazonoyl)bis-(acetamide) ((*E*)-**3f**; $C_{12}H_{15}N_5O_2$)

Yield: 60% of yellowish crystals; m.p.: 150–152°C (EtOH-hexane); MS: *m/z* = 261 (M^+, 0.5%), 218 (38), 204 (30), 176 (43), 162 (25), 134 (100), 106 (31), 105 (28), 104 (39), 79 (33), 78 (80), 77 (42), 58 (21), 52 (58), 51 (95), 59 (38); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 2.11 (s, 3H, $COCH_3$), 2.18 (s, 3H, $COCH_3$), 2.37 (s, 3H, CH_3), 7.43 (m, 1H, Py H-5), 8.28 (m, 1H, Py H-4), 8.59 (m, 1H, Py H-6), 9.13 (m, 1H, Py H-2), 9.96 (s, 1H, NH), 10.46 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 14.6 (CH_3, ^1J(CH_3) = 128.7 Hz), 24.0 (CO*C*H_3, ^1J(CH_3) = 128.9 Hz), 24.7 (CO*C*H_3, ^1J(CH_3) = 128.9 Hz), 123.2 (Py C-5), 133.5 (Py C-3), 134.1 (Py C-4), 144.4 (N=C–N), 148.1 (Py C-2), 150.2 (Py C-6), 158.9 (ArC=N), 169.7 (*C*OCH_3, ^2J(CO, CH_3) = 6.5 Hz), 169.9 (*C*OCH_3, ^2J(CO,CH_3) = 6.5 Hz) ppm.

N-Acetyl-N′-((E)-1-(2-furyl)ethylidene)aminomethanehydrazonamide acetate
((*E*)-**4c** · HOAc; $C_{11}H_{16}N_4O_4$)

Compound **4c** · HOAc resulted (besides **3c**) from fractional crystallisation of the crude product obtained upon reaction of **2c** with acetic anhydride.

Yield: 10% of yellow crystals; m.p.: 81°C (EtOH); MS: *m/z* = 208 (M^+-HOAc, 56%), 193 (39), 151 (51), 95 (28), 94 (55), 67 (20), 66 (100), 58 (24), 55 (22), 45 (35); ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 1.90 (s, 3H, CH_3COO), 2.05 (s, 3H, $NCOCH_3$), 2.20 (s, 3H, CH_3), 6.54 (dd, ^3J(H3, H4) = 3.4 Hz, ^3J(H4, H5) = 1.8 Hz, 1H, furane H-4), 6.87 (dd, ^3J(H3, H4) = 3.4 Hz, ^4J(H3, H5) = 0.7 Hz, furane H-3), 7.60 (broad s, 1H, NH), 7.69 (dd, ^3J(H4, H5) = 1.8 Hz, ^4J(H3,

H5) = 0.7 Hz, 1H, furane H-5), 9.0–12.0 (broad s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 13.4 (CH_3, $^1J(CH_3) = 128.5$ Hz), 21.0 ($COCH_3$, $^1J(CH_3) = 128.8$ Hz), 23.9 ($COCH_3$, $^1J(CH_3) = 128.8$ Hz), 108.9 (furane C-3, ^1J(C3, H3) = 176.2 Hz, ^2J(C3, H4) = 4.5 Hz, ^3J(C3, H5) = 5.7 Hz), 111.7 (furane C-4, ^1J(C4, H4) = 175.3 Hz, ^2J(C4, H3) = 4.3 Hz, ^2J(C4, H5) = 13.3 Hz), 143.3 (furane C-5, ^1J(C5, H5) = 204.0 Hz, ^2J(C5, H4) = 10.9 Hz, ^3J(C5, H3) = 7.7 Hz), 146.5 (ArC=N, ^2J(C=N, CH_3) = 6.5 Hz), 153.5 (furane C-2), 154.5 (N=C–N), 172.0 ($COCH_3$), 172.2 ($COCH_3$) ppm.

X-Ray structure determinations of **2c**, **2d**, **3b**, *and* **3f**

Crystal data and experimental details are given in Table 1. X-ray data were collected on a Siemens Smart CCD area detector diffractometer (graphite monochromated MoK_α radiation, $\lambda = 0.71073$ Å, sealed X-ray tube, nominal crystal-to-detector distance 38.55 mm, 0.3°ω-scan frames, complete spheres of the reciprocal space recorded). Corrections for *Lorentz* and polarization effects, for crystal decay, and for absorption (multi-scan type; program SADABS [22]) were applied. The structures were solved with direct methods using the program SHELXS97 [22]. Structure refinements on F^2 were carried out with the program SHELXL93 [22]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located from difference *Fourier* maps and were inserted in calculated positions in case of aromatic or methyl hydrogen atoms, whereas N-bonded hydrogen atoms were refined in *x*, *y*, *z*. The isotropic temperature factors of the hydrogen atoms were fixed at $1.2 \times U_{eq}$ of their carrier atoms ($1.5 \times U_{eq}$ for CH_3). For the thiophene containing compounds **2d** and **3d**, bimodal orientations of the thiophene rings were encountered. For **2d** this feature was modeled by refining two alternative thiophene ring orientations with final population frequencies of 88.0(2)% and 12.0(2)%. For **3d** only the occupancy of S was refined (occupancy factor 0.957(2)). Further details of the crystal structure determinations are available from the Fachinformationszentrum Karlsruhe GmBH, D-76344 Eggenstein-Leopoldshafen (Germany), on quoting the depository numbers CSD-410492 (**2c**), 410493 (**2d**), 410491 (**3b**), 410495 (**3d**), and 410494 (**3f**), the names of the authors, the title of the paper, and the journal.

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