Diazine-Derived Guanidines, Isothioureas, and Isoureas: Synthesis and Attempts of Configurational Assignment

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Received November 16, 2001

The utility of diazinyl substituted carbodiimides (**1a-c**) for the synthesis of novel guanidines (**2**), isothioureas (**3**), and isoureas (**4**) is shown. Attempts to determine the stereochemistry of the target compounds using NOE difference spectroscopy or X-ray analysis, respectively, are described.

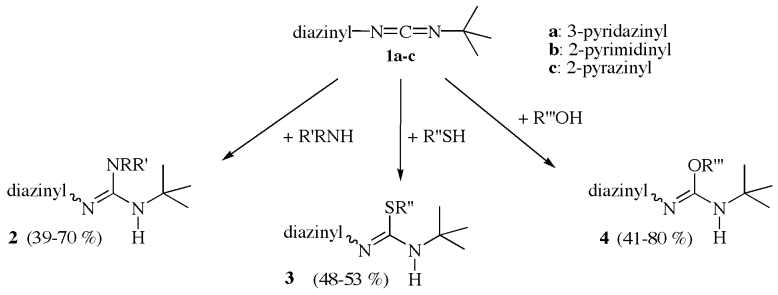
J. Heterocyclic Chem., **39**, 695 (2002).

Recently, we have described the synthesis of a series of novel diazinyl substituted carbodiimides of type **1** by reaction of a thiourea derivative with methyl iodide and base in a two phase system [1]. Whereas it is well known from the literature that phenyl and azinyl substituted carbodiimides represent useful building blocks for the synthesis of a variety of carbonic acid derivatives like guanidines, isothioureas, and isoureas [2,3], so far diazine isosters were not prepared starting from compounds of type **1**. Considering that such a carbonic acid substructure is abundant in various pharmacologically active compounds (*e.g.* antihypertensive agents [4,5,6a/b], H_2 histamine receptor antagonists [7,8a/b], H_3 histamine receptor agonists and antagonists [9a/b], NO synthase inhibitors [10], anti-inflammatory agents [11a-c], Na^+/H^+-exchange inhibitors [12], Na^+/Ca^{2+}-exchange inhibitors [13], and NMDA receptor antagonists [14], respectively), we wanted to investigate the synthetic potential of the diazinyl substituted carbodiimides.

The synthesis of the desired compounds, which act as model substances, was performed by reaction of the appropriate carbodiimide **1a-c** with NH-, SH-, and OH-nucleophiles under mild conditions (room temperature to 50 °C, Scheme 1). In order to investigate the synthetic potential in a wide range, not only aliphatic, aromatic, and araliphatic nucleophiles were employed but also the diazine moiety was varied.

Guanidines of type **2** were accessible in moderate yields by reaction of the appropriate carbodiimide with ammonia, primary, and secondary (aliphatic as well as aromatic) amines at room temperature (2-3 hours). However, treatment of the carbodiimide **1b** with a *S*-nucleophile (benzylmercaptane) under the same conditions (3 hours at room temperature) did not lead in the formation of the target compound **3bb**. On the other hand, the isothiourea derivative **3bb** could be obtained in the presence of $CuCl_2$ at 50 °C after 3 hours. This catalyst was chosen since it is known from the literature [3] that certain copper salts are effective as catalysts for the addition of alcohols or thiols on carbodiimides. Moreover, using this procedure enabled us to prepare the corresponding *S*-arylisothiourea **3aa** in moderate yield.

Scheme 1



No	diazinyl	R and R'
2aa	3-pyridazinyl	R = R' = H
2ab	3-pyridazinyl	R = H; R' = C_3H_7
2cc	2-pyrazinyl	R = R' = C_2H_5
2bd	2-pyrimidinyl	R = H; R' = CH_2-C_6H_4(4-OCH_3)
2ae	3-pyridazinyl	R = H; R' = C_6H_5
2cf	2-pyrazinyl	R = CH_3; R' = C_6H_5

No	diazinyl	R"
3aa	3-pyridazinyl	R" = C_6H_4(2-NH_2)
3bb	2-pyrimidinyl	R" = CH_2-C_6H_5

No	diazinyl	R'"
4aa	3-pyridazinyl	R'" = C_2H_5
4cb	2-pyrazinyl	R'" = C_6H_5

For the synthesis of the *O*-alkyl and -arylisoureas **4aa** and **4cb** employment of $CuCl_2$ was useful again. Therefore, the *O*-phenylisourea derivative **4cb** was accessible in 80 % yield by treatment of **1c** with phenol in 1,4-dioxane at room temperature (3 hours). **4aa** was obtained by reaction of **1a** in ethanol in the presence of the catalyst. In order to verify if the addition of a non-basic nucleophile also takes place in the absence of $CuCl_2$, **1a** was stirred at room temperature in ethanol. After 1 week under these conditions, no starting material could be detected and **4aa** was isolated in 28 % yield.

In view of the presented high synthetic utility of the diazinyl substituted carbodiimides and the biological activities described for guanidines and iso(thio)ureas, **1a-c** can be considered as versatile building blocks for compounds of pharmaceutical interest. Moreover, it should be noted that isourea as well as *S*-aryliosothiourea derivatives can not be prepared starting from the appropriate (thio)urea compound by alkylation or arylation, respectively.

The structures of all novel compounds were confirmed by elemental analyses, ir, and nmr spectroscopy as well as ms data (see experimental part). It should be emphasised that the target compounds can exist in the *E*- or *Z*-form, or as mixtures of *E*/*Z*-isomers. According to the ^{1}H-nmr spectra, all derivatives except **2ab** turned out to be single iso-

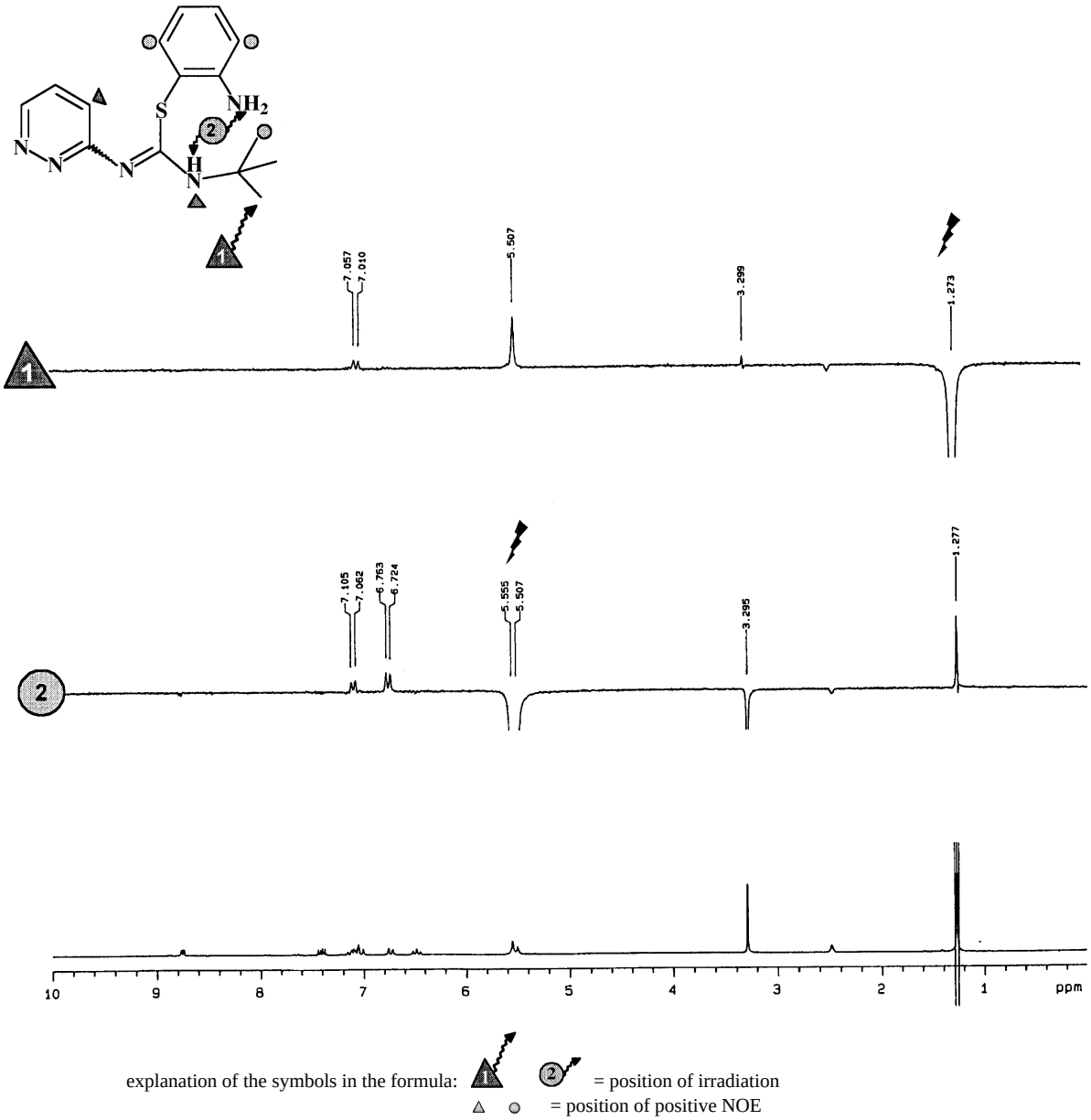


Figure 1a. ^{1}H-NMR and NOE difference spectra of **3aa.**

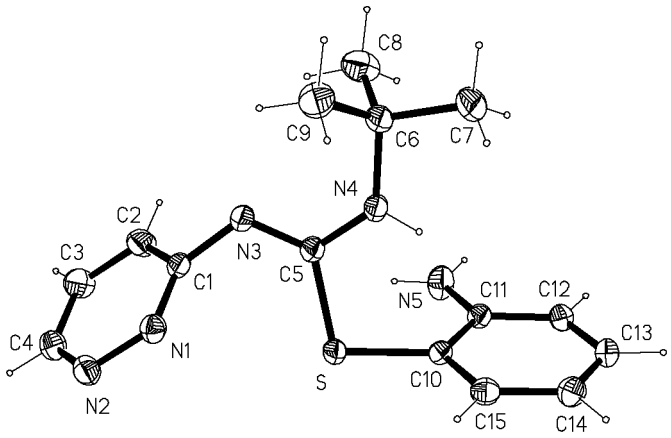


Figure 1b. Molecular structure of **3aa** in crystalline state (20% ellipsoids). Selected bond lengths and angles (Å, deg): N1-N2 1.353(2), C1-N3 1.400(2), C5-N3 1.289(2), C5-N4 1.343(2), C5-S 1.819(2), N4-C6 1.484(2), S-C10 1.775(2), C1-N3-C5 121.7(1), N3-C5-N4 123.8(1), N3-C5-S 121.1(1), N4-C5-S 115.2(1), C5-S-C10 101.7(1), C5-N3-C1-N1 57.8(2), C5-S-C10-C11 –78.5(1).

mers. Based on previous findings in our group homonuclear NOE difference spectroscopy is a convenient method permitting the rapid determination of the stereochemistry of compounds containing the C=N substructure [15a-c]. In the case of the pyrimidinyl congeners **2bd** and **3bb** this technique could not be employed since there is no α-CH on the heteroarene.

The spectra of the NOE experiments of a pyridazinyl substituted derivative (exemplary, the isothiourea **3aa** was chosen) are shown in Figure 1a. Upon irradiation of the *tert*-butyl protons (δ=1.27 ppm), a marked NOE on the pyridazine-H4 was observed. Moreover irradiation of the NH/NH_2 (δ=5.51/5.56 ppm) resonances resulted in a positive NOE on the *tert*-butyl and phenyl-H3 protons. Since these results did not permit the assignment of the stereochemistry, an X-ray analysis of **3aa** was performed, thus clearly indicating *Z*-configuration (see Figure 1b).

In case of a pyrazinyl substituted congener (**2cf**), irradiation of the *tert*-butyl protons (δ=1.39 ppm) leads to a marked enhancement of the NH, phenyl-H2/H6, and pyrazine-H3 signal, perturbing the NH transition (δ=6.90 ppm) enhances the *tert*-butyl signal. Moreover, upon irradiation of the *N*-methyl signal (δ=3.02 ppm), a marked increase of the NH, phenyl-H2/H6, and pyrazine-H3 signal was observed (see Figure 2a). Whereas these results did not allow us to determine the stereochemistry, an X-ray analysis enabled us to assign the correct configuration of **2cf** (see Figure 2b).

In summary, diazinyl substituted carbodiimides of type **1** represent versatile precursors for novel potential drug substances; further investigations on this subject are intended. In the series of the diazinyl substituted carbonic acid derivatives NOE experiments did not permit the unequivocal determination of stereochemistry. For the pyridazinyl and pyrazinyl congeners, the failure may be attributed due to the possibility of tautomerism and the formation of intramolecular hydrogen bonds, respectively. The assignment of the configuration, however, can be achieved by means of X-ray analysis.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage microscope (Reichert) and are uncorrected. Solvents were purified by distillation from the indicated drying agent: 1,4-dioxane (Na); ethanol (Na, diethyl phthalate). All reactions were run under a dry nitrogen atmosphere. Infrared spectra (KBr pellets) were recorded on a Mattson Galaxy Series FTIR 3000 spectrophotometer. Mass spectra were obtained on a Finnigan MAT SSQ 7000 spectrometer (EI, 70 eV). All NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ solution in 5 mm tubes at 30 °C on a Varian Gemini 200 spectrometer (199.98 MHz for ^1H, 50.29 MHz for ^{13}C) with the deuterium signal of the solvent as the lock and TMS as internal standard. Chemical shifts are expressed in parts per million. The standard Varian program NOEDIF was used to generate NOE. DEPT spectra were run in a standard manner using only the θ = 135° pulse to separate the CH/CH_3 and CH_2 lines phased "up" and "down", respectively. Reactions were monitored by tlc using Polygram® SIL G/UV_{254} (Macherey-Nagel) plastic-backed plates (0.25 mm layer thickness). Light petroleum refers to the fraction of bp 40-60 °C. Elemental analyses were performed by Mag. J. Theiner, Institute of Physical Chemistry, University of Vienna, Austria.

Starting Materials.

Compounds not listed below were commercial samples of good grade. 1,1-Dimethylethyl-diazinyl-carbodiimides were prepared in analogy to ref [1] and used without further purification.

N-(1,1-Dimethylethyl)-*N'*-(3-pyridazinyl)guanidine (**2aa**).

N-(1,1-Dimethylethylcarbonimidoyl)-3-pyridazinamine (**1a**) (480 mg, 2.72 mmol) was dissolved in 10 mL of 1,4-dioxane, which shortly before had been saturated with gaseous ammonia, and the mixture was stirred for 24 hours at room temperature. The solvent was removed *in vacuo* and the remaining residue was purified by column chromatography (silica gel, dichloromethane/ethanol, 1:1) followed by recrystallisation from diisopropylether/ethyl acetate. Yield: 206 mg (39%) of beige crystals, mp 158-161 °C; IR ν 3376, 3214 (NH), 1630 (CN) cm^{-1}; ^1H-NMR (DMSO-d_6): δ 8.50 (dd, 1H, J_{46} = 1.5 Hz, J_{56} = 4.4 Hz, pyridazine H-6), 7.51 (br s, 2H, NH_2), 7.29 (dd, 1H, J_{45} = 8.9 Hz, J_{56} = 4.4 Hz, pyridazine H-5), 6.85 (dd, 1H, J_{45} = 8.9 Hz, J_{46} = 1.5 Hz, pyridazine H-4), 6.24 (br s, 1H, NH), 1.38 [s, 9H, $C(CH_3)_3$]; ^1H-NMR ($CDCl_3$): δ 8.55 (dd, 1H, J_{46} = 1.5 Hz, J_{56} = 4.5 Hz, pyridazine H-6), 7.20 (dd, 1H, J_{45} = 8.9 Hz, J_{56} = 4.5 Hz, pyridazine H-5), 6.95 (dd, 1H, J_{45} = 8.9 Hz, J_{46} = 1.5 Hz, pyridazine H-4), 1.46 [s, 9H, $C(CH_3)_3$]; ^{13}C-NMR ($CDCl_3$) δ 164.7 (pyridazine C-3), 156.2 (C=N), 144.3 (pyridazine C-6), 127.3 (pyridazine C-5), 124.9 (pyridazine C-4), 50.8 [$C(CH_3)_3$], 29.9 [$C(CH_3)_3$]; MS *m/z* % 193.1 (M^+, 80).

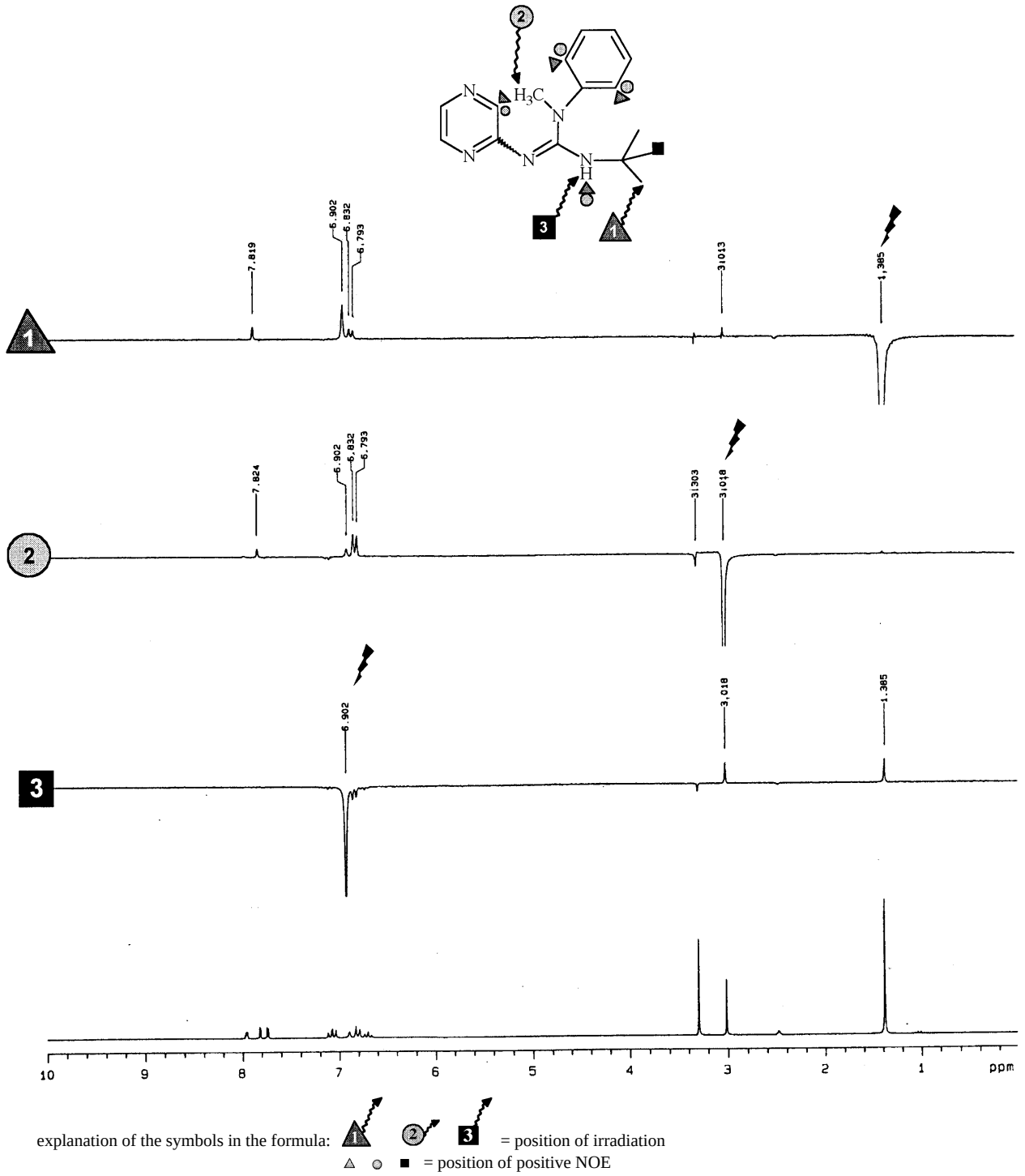


Figure 2a. ^{1}H-NMR and NOE difference spectra of **2cf**.

Anal. Calcd for $C_9H_{15}N_5$: C, 55.94; H, 7.82; N, 36.24; Found: C, 55.69; H, 7.57; N, 35.98.

General Procedure for the Reaction of 1,1-Dimethylethyl-diazinyl-carbodiimide with Volatile Aliphatic Amines.

The appropriate 1,1-dimethylethyl-diazinyl-carbodiimide (**1**) (245 mg, 1.39 mmol) was dissolved in *n*-propylamine (1.65 g, 27.8 mmol) or diethylamine (2.03 g, 27.8 mmol), respectively, and stirred for 2 hours at room temperature. The solvent was removed *in vacuo* and the remaining residues were treated as follows:

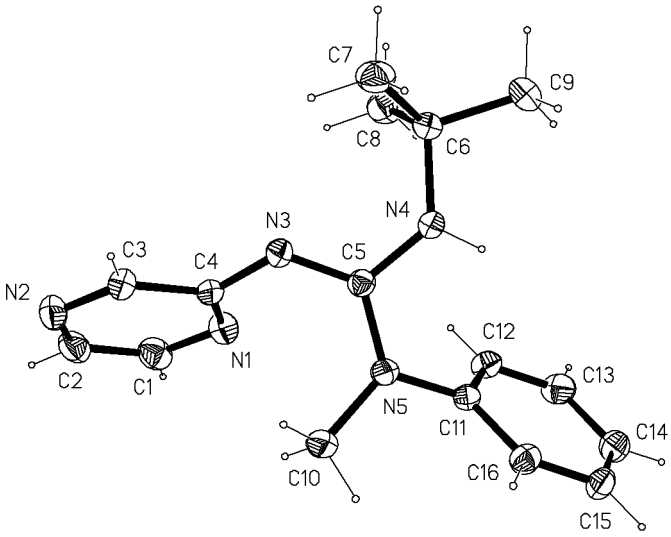


Figure 2b. Molecular structure of **2cf** in crystalline state (20% ellipsoids). Selected bond lengths and angles (Å, deg): C4-N3 1.370(2), C5-N3 1.299(2), C5-N4 1.351(1), C5-N5 1.376(1), N4-C6 1.475(2), N5-C10 1.457(1), N5-C11 1.427(2), C4-N3-C5 123.1(1), N3-C5-N4 119.2(1), N3-C5-N5 125.0(1), N4-C5-N5 115.4(1), C5-N5-C11 121.8(1), C5-N3-C4-N1 –33.6(2), C5-N5-C11-C12 –53.8(2).

N-(1,1-Dimethylethyl)-*N'*-propyl-*N''*-(3-pyridazinyl)guanidine (**2ab**).

The residue was purified by column chromatography (silica gel, ethyl acetate) followed by recrystallisation from diisopropylether/light petroleum. Yield: 142 mg (43%) of light yellow crystals, mp 106-115 °C; IR ν 3313 (NH), 1622 (CN) cm^{-1}; NMR analysis revealed this product to be a 4:1 mixture of stereoisomers (**2ab/1** and **2ab/2**).

Compound (**2ab/1**) has ^{1}H-NMR (DMSO-d_6): δ 8.90-8.60 (br, 1H, NH-butyl), 8.45 (dd, 1H, J_{46} = 1.6 Hz, J_{56} = 4.5 Hz, pyridazine H-6), 7.26 (dd, 1H, J_{45} = 8.9 Hz, J_{56} = 4.5 Hz, pyridazine H-5), 7.00-6.60 (br, 1H, NH-propyl), 6.83 (dd, 1H, J_{45} = 8.9 Hz, J_{46} = 1.6 Hz, pyridazine H-4), 3.27-3.17 (m, 2H, N-CH_2), 1.64-1.46 (m, 2H, CH_2), 1.41 [s, 9H, C(CH_3)$_3$], 0.91 (t, 3H, J = 7.4 Hz, CH_3); ^{1}H-NMR ($CDCl_3$): δ 8.50 (dd, 1H, J_{46} = 1.6 Hz, J_{56} = 4.4 Hz, pyridazine H-6), 7.15 (dd, 1H, J_{45} = 9.0 Hz, J_{56} = 4.4 Hz, pyridazine H-5), 6.95 (dd, 1H, J_{45} = 9.0 Hz, J_{46} = 1.6 Hz, pyridazine H-4), 3.25-3.16 (m, 2H, N-CH_2), 1.77-1.59 (m, 2H, CH_2), 1.48 [s, 9H, C(CH_3)$_3$], 1.02 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C-NMR ($CDCl_3$): δ 164.8 (pyridazine C-3), 154.8 (C=N), 143.8 (pyridazine C-6), 126.8, 125.7 (pyridazine C-4, pyridazine C-5), 51.1 [*C*(CH_3)$_3$], 43.3 (*C*H_2CH$_2$CH$_3$), 30.0 [C(*C*H_3)$_3$], 22.7 (CH$_2$*C*H$_2$CH$_3$), 11.7 (CH$_2$CH$_2$*C*H$_3$).

Compound (**2ab/2**) has ^{1}H-NMR (DMSO-d_6): δ 9.27 (br s, 1H, NH-propyl), 8.76 (dd, 1H, J_{46} = 1.6 Hz, J_{56} = 4.7 Hz, pyridazine H-6), 7.84 (dd, 1H, J_{45} = 9.1 Hz, J_{46} = 1.6 Hz, pyridazine H-4), 7.56 (br s, 1H, NH-butyl), 7.52 (dd, 1H, J_{45} = 9.1 Hz, J_{56} = 4.7 Hz, pyridazine H-5), 3.27-3.17 (m, 2H, N-CH_2), 1.64-1.46 (m, 2H, CH_2), 1.32 [s, 9H, C(CH_3)$_3$], 0.91 (t, 3H, J = 7.4 Hz, CH_3); ^{1}H-NMR ($CDCl_3$): δ 11.30 (br s, 1H, NH), 8.67 (dd, 1H, J_{46} = 1.4 Hz, J_{56} = 4.6 Hz, pyridazine H-6), 8.26 ("d", 1H, pyridazine H-4), 7.50 (br s, 1H, NH), 7.41 (dd, 1H, J_{45} = 9.2 Hz, J_{56} = 4.6 Hz, pyridazine H-5), 3.25-3.16 (m, 2H, N-CH_2), 1.77-1.59 (m, 2H, CH_2), 1.47 [s, 9H, C(CH_3)$_3$], 1.02 (t, 3H, J = 7.3 Hz, CH_3); ^{13}C-NMR ($CDCl_3$): δ 157.6, 154.3 (pyridazine C-3, C=N), 145.5 (pyridazine C-6), 128.7 (pyridazine C-5), 118.2 (pyridazine C-4), 50.9 [*C*(CH_3)$_3$], 43.3 (*C*H_2CH$_2$CH$_3$), 29.1 [C(*C*H_3)$_3$], 22.7 (CH$_2$*C*H$_2$CH$_3$), 11.7 (CH$_2$CH$_2$*C*H$_3$). MS *m/z* % 235.2 (M^+, 62).

Anal. Calcd for $C_{12}H_{21}N_5$: C, 61.25; H, 8.99; N, 29.76; Found: C, 61.45; H, 8.79; N, 29.97.

N,*N*-(Diethyl)-*N'*-(1,1-dimethylethyl)-*N''*-(2-pyrazinyl)guanidine (**2cc**).

The residue was purified by column chromatography (silica gel, ethyl acetate) followed by recrystallisation from ethanol/water. Yield: 170 mg (49%) of colorless crystals, mp 92-97 °C; IR ν 3268 (NH), 1552 (CN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.99 (dd, 1H, J_{36} = 1.5 Hz, J_{56} = 2.7 Hz, pyrazine H-6), 7.79 (d, 1H, J_{36} = 1.5 Hz, pyrazine H-3), 7.70 (d, 1H, J_{56} = 2.7 Hz, pyrazine H-5), 6.03 (br s, 1H, NH), 3.04 (q, 4H, J = 7.4 Hz, 2x CH_2), 1.26 [s, 9H, C(CH_3)$_3$], 0.96 (t, 6H, J = 7.4 Hz, 2x CH_3); ^{1}H-NMR ($CDCl_3$): δ 8.09-8.08 (m, 2H, pyrazine H), 7.87-7.85 (m, 1H, pyrazine H), 5.67 (br s, 1H, NH), 3.26 (q, 4H, J = 7.1 Hz, 2x CH_2), 1.30 [s, 9H, C(CH_3)$_3$], 1.11 (t, 6H, J = 7.1 Hz, 2x CH_3); ^{13}C-NMR ($CDCl_3$): δ 158.8, 158.1 (pyrazine C-2, C=N), 141.5, 141.2, 133.9 (pyrazine C-3, pyrazine C-5, pyrazine C-6), 53.0 [*C*(CH_3)$_3$], 43.1 (2x CH_2), 29.9 [C(*C*H_3)$_3$], 12.8 (2x CH_3); MS *m/z* % 249.2 (M^+, 75).

Anal. Calcd for $C_{13}H_{23}N_5$: C, 62.62; H, 9.30; N, 28.09; Found: C, 62.92; H, 9.06; N, 28.04.

N-(4-Methoxybenzyl)-*N'*-(1,1-dimethylethyl)-*N''*-(2-pyrimidinyl)guanidine (**2bd**).

4-Methoxybenzylamine (242 mg, 1.76 mmol) was added to a solution of 1,1-dimethylethyl-pyrimidin-2-yl-carbodiimide (**1b**) (345 mg, 1.96 mmol) in 5 mL of 1,4-dioxane and the mixture was stirred for 3 hours at room temperature. The solvent was removed *in vacuo* and the remaining residue was washed 2-3 times with diethylether to provide crystals, which were recrystallised from diisopropylether. Yield: 340 mg (62%) of colorless crystals, mp 138-140 °C; IR ν 3308 (NH), 1617 (CN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 8.37 (d, 2H, $J_{45=56}$ = 4.8 Hz, pyrimidine H-4/6), 8.18 (br, 1H, NH-CH_2), 7.80 (br, 1H, NH-butyl), 7.28-7.22 (m, 2H, phenyl H-2/6), 6.92-6.85 (m, 2H, phenyl H-3/5), 6.69 (t, 1H, $J_{45=56}$ = 4.8 Hz, pyrimidine H-5), 4.47 ("br s", 2H, CH_2), 3.71 (s, 3H, OCH_3), 1.38 [s, 9H, C(CH_3)$_3$]; ^{1}H-NMR ($CDCl_3$): δ 8.42 (d, 2H, $J_{45=56}$ = 4.7 Hz, pyrimidine H-4/6), 7.60-7.00 (br, 2H, 2x NH), 7.31-7.27 (m, 2H, phenyl H-2/6), 6.91-6.87 (m, 2H, phenyl H-3/5), 6.59 (t, 1H, $J_{45=56}$ = 4.7 Hz, pyrimidine H-5), 4.51 (d, 2H, J = 4.6 Hz, CH_2), 3.81 (s, 3H, OCH_3), 1.40 [s, 9H, C(CH_3)$_3$]; ^{13}C-NMR ($CDCl_3$): δ 166.0, 159.1, 156.2 (pyrimidine C-2, C=N, phenyl C-4), 157.1 (pyrimidine C-4/6), 130.3 (phenyl C-1), 128.7 (phenyl C-2/6), 114.2 (phenyl C-3/5), 111.3 (pyrimidine C-5), 55.3 (OCH_3), 50.9 [*C*(CH_3)$_3$], 45.3 (CH_2), 30.0 [C(*C*H_3)$_3$]; MS *m/z* % 313.2 (M^+, 60).

Anal. Calcd for $C_{17}H_{23}N_5O$: C, 65.15; H, 7.40; N, 22.35; Found: C, 65.34; H, 7.35; N, 22.10.

General Procedure for the Reaction of 1,1-Dimethylethyl-diazinyl-carbodiimides with Aromatic Amines.

Aniline (175 mg, 1.87 mmol) or *N*-methylaniline (200 mg, 1.87 mmol), respectively, was added to a solution of the appropriate 1,1-dimethylethyl-diazinyl-carbodiimide (**1**) (220

mg, 1.25 mmol) in 5 mL of 1,4-dioxane and the mixture was stirred for 3 hours at room temperature. The solvent was removed *in vacuo* and the remaining residues were treated as follows:

N-(1,1-Dimethylethyl)-*N*'-phenyl-*N*"-(3-pyridazinyl)guanidine (**2ae**).

The residue was purified by column chromatography (silica gel, dichloromethane/ethyl acetate, 4:1) followed by recrystallisation from diisopropylether Yield: 182 mg (54%) of colorless crystals, mp 155-157 °C; IR ν 3283 (NH), 1620 (CN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 10.75 (br s, 1H, NH-phenyl), 8.57 ("d", 1H, pyridazine H-6), 7.41 (dd, 1H, J_{45} = 8.8 Hz, J_{56} = 4.4 Hz, pyridazine H-5), 7.32-6.97 (m, 6H, pyridazine H-4, phenyl H), 6.31 (br s, 1H, NH-butyl), 1.43 [s, 9H, $C(CH_3)_3$]; ^{1}H-NMR ($CDCl_3$): δ 11.81 (br s, 1H, NH), 8.55 (dd, 1H, J_{46} = 1.6 Hz, J_{56} = 4.4 Hz, pyridazine H-6), 7.42-7.14 (m, 6H, pyridazine H-5, phenyl H), 7.06 (dd, 1H, J_{45} = 8.9 Hz, J_{46} = 1.6 Hz, pyridazine H-4), 4.75 (br s, 1H, NH), 1.45 [s, 9H, $C(CH_3)_3$]; ^{13}C-NMR ($CDCl_3$): δ 164.3 (pyridazine C-3), 152.0 (C=N), 144.2 (pyridazine C-6), 137.8 (phenyl C-1), 129.6, 127.1, 125.9, 125.4 (phenyl C-2/6, phenyl C-3/5, phenyl C-4, pyridazine C-4, pyridazine C-5), 51.6 [*C*$(CH_3)_3$], 29.6 [C(*C*$H_3)_3$]; MS *m/z* % 269.2 (M^+, 86).

Anal. Calcd for $C_{15}H_{19}N_5$: C, 66.89; H, 7.11; N, 26.00; Found: C, 67.11; H, 7.29; N, 26.03.

(Z)-*N*-(1,1-Dimethylethyl)-*N*'-methyl-*N*'-phenyl-*N*"-(2-pyrazinyl)guanidine (**2cf**).

The residue was purified by column chromatography (silica gel, diethylether) followed by recrystallisation from diisopropylether/light petroleum. Yield: 246 mg (70%) of colorless crystals, mp 106-108 °C; IR ν 3492 (NH), 1562 (CN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.96 (dd, 1H, J_{36} = 1.5 Hz, J_{56} = 2.6 Hz, pyrazine H-6), 7.82 (d, 1H, J_{36} = 1.5 Hz, pyrazine H-3), 7.74 (d, 1H, J_{56} = 2.6 Hz, pyrazine H-5), 7.12-7.04 (m, 2H, phenyl H-3/5), 6.90 (br s, 1H, NH), 6.84-6.80 (m, 2H, phenyl H-2/6), 6.74-6.67 (m, 1H, phenyl H-4), 3.02 (s, 3H, CH_3), 1.39 [s, 9H, $C(CH_3)_3$]; ^{1}H-NMR ($CDCl_3$): δ 8.14 (d, 1H, J_{36} = 1.6 Hz, pyrazine H-3), 8.09 (dd, 1H, J_{36} = 1.6 Hz, J_{56} = 2.8 Hz, pyrazine H-6), 7.89 (d, 1H, J_{56} = 2.8 Hz, pyrazine H-5), 7.32-7.23 (m, 2H, phenyl H-3/5), 7.12-6.98 (m, 3H, phenyl H-2/6, phenyl H-4), 5.60 (br s, 1H, NH), 3.06 (s, 3H, CH_3), 1.32 [s, 9H, $C(CH_3)_3$]; ^{13}C-NMR ($CDCl_3$): δ 158.3, 156.1 (pyrazine C-2, C=N), 146.0 (phenyl C-1), 141.8, 141.3, 135.3 (pyrazine C-3, pyrazine C-5, pyrazine C-6), 129.2 (phenyl C-3/5), 123.5 (phenyl C-4), 122.2 (phenyl C-2/6), 52.6 [*C*$(CH_3)_3$], 39.9 (CH_3), 29.4 [C(*C*$H_3)_3$]; MS *m/z* % 283.2 (M^+, 33).

Anal. Calcd for $C_{16}H_{21}N_5$: C, 67.82; H, 7.47; N, 24.71; Found: C, 68.06; H, 7.62; N, 24.89.

(Z)-*S*-(2-Aminophenyl)-*N*-(1,1-dimethylethyl)-*N*'-(3-pyridazinyl)isothiourea (**3aa**).

2-Aminothiophenol (195 mg, 1.55 mmol) was added to a solution of 1,1-dimethylethyl-pyridazin-3-yl-carbodiimide (**1a**) (170 mg, 1.04 mmol) in 5 mL of 1,4-dioxane and the mixture was stirred for 3 hours at room temperature. The solvent was removed *in vacuo* and the remaining residue was purified by column chromatography (silica gel, dichloromethane/ethyl acetate, 5:1) followed by recrystallisation from diisopropylether/ethyl acetate. Yield: 150 mg (48%) of beige crystals, mp 146-150 °C; IR ν 3461, 3385, 3287 (NH), 1609 (CN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 8.76 (dd, 1H, J_{46} = 1.5 Hz, J_{56} = 4.8 Hz, pyridazine H-6), 7.41 (dd, 1H, J_{45} = 8.8 Hz, J_{56} = 4.8 Hz, pyridazine H-5), 7.16-7.03 (m, 3H, phenyl H, pyridazine H-4), 6.75 (dd, 1H, J = 8.2 Hz, J = 0.9 Hz, phenyl H-3), 6.53-6.45 (m, 1H, phenyl H), 5.56 (br s, 2H, NH_2), 5.51 (br s, 1H, NH), 1.27 [s, 9H, $C(CH_3)_3$]; ^{1}H-NMR ($CDCl_3$): δ 8.81 (dd, 1H, J_{46} = 1.6 Hz, J_{56} = 4.6 Hz, pyridazine H-6), 7.39-7.17 (m, 3H, pyridazine H-5, phenyl H), 7.06 (dd, 1H, J_{45} = 8.7 Hz, J_{46} = 1.6 Hz, pyridazine H-4), 6.76-6.66 (m, 2H, phenyl H-3), 4.84 (br s, 1H, NH), 4.64 (br s, 2H, NH_2), 1.32 [s, 9H, $C(CH_3)_3$]; ^{13}C-NMR ($CDCl_3$): δ 163.1 (pyridazine C-3), 149.4 (C=N, phenyl C-2), 146.6 (pyridazine C-6), 137.5, 132.1 (phenyl C-4, phenyl C-6), 127.3 (pyridazine C-5), 123.1, 118.6, 115.3 (pyridazine C-4, phenyl C-3, phenyl C-5), 111.9 (phenyl C-1), 53.7 [*C*$(CH_3)_3$], 28.4 [C(*C*$H_3)_3$]; MS *m/z* % 301.1 (M^+, 24).

Anal. Calcd for $C_{15}H_{19}N_5S$: C, 59.77; H, 6.35; N, 23.23; Found: C, 60.07; H, 6.35; N, 23.22.

S-Benzyl-*N*-(1,1-dimethylethyl)-*N*'-(2-pyrimidinyl)isothiourea (**3bb**).

Benzylmercaptane (1900 mg, 15.3 mmol) and catalytic amounts of copper(II)chloride were added to a solution of 1,1-dimethylethyl-pyrimidin-2yl-carbodiimide (**1b**) (269 mg, 1.53 mmol) in 5 mL of 1,4-dioxane and the mixture was heated to 50 °C for 5 hours. After cooling the solvent was removed *in vacuo* and the remaining residue was purified by column chromatography (silica gel, diethylether) followed by recrystallisation from diisopropylether/ light petroleum. Yield: 242 mg (53%) of colorless crystals, mp 76-80 °C; IR ν 3259, 3147 (NH), 1578 (CN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 8.54 (d, 2H, $J_{45=56}$ = 4.7 Hz, pyrimidine H-4/6), 7.58 (br, 1H, NH), 7.34-7.21 (m, 5H, phenyl H), 6.95 (t, 1H, $J_{45=56}$ = 4.7 Hz, pyrimidine H-5), 4.17 (s, 2H, CH_2), 1.34 [s, 9H, $C(CH_3)_3$]; ^{1}H-NMR ($CDCl_3$): δ 10.16 (br, 1H, NH), 8.55 (d, 2H, $J_{45=56}$ = 4.8 Hz, pyrimidine H-4/6), 7.45-7.19 (m, 5H, phenyl H), 6.79 (t, 1H, $J_{45=56}$ = 4.8 Hz, pyrimidine H-5), 4.46 (s, 2H, CH_2), 1.46 [s, 9H, $C(CH_3)_3$]; ^{13}C-NMR ($CDCl_3$): δ 164.4 (pyrimidine C-2, C=N), 157.3 (pyrimidine C-4/6), 136.9 (phenyl C-1), 129.3, 128.5 (phenyl C-2/6, phenyl C-3/5), 127.2 (phenyl C-4), 113.7 (pyrimidine C-5), 52.9 [*C*$(CH_3)_3$], 36.4 (CH_2), 29.4 [C(*C*$H_3)_3$]; MS *m/z* % 300.1 (M^+, 4).

Anal. Calcd for $C_{16}H_{20}N_4S$ x 0.4 H_2O: C, 62.47; H, 6.82; N, 18.21; Found: C, 62.36; H, 6.65; N, 18.36.

O-Ethyl-*N*-(1,1-dimethylethyl)-*N*'-(3-pyridazinyl)isourea (**4aa**).

1,1-Dimethylethyl-pyridazin-3-yl-carbodiimide (**1a**) (215 mg, 1.22 mmol) was dissolved in 5 mL of ethanol and the mixture was heated to 50 °C for 3 hours. After cooling the solvent was removed *in vacuo* and the remaining residue was purified by column chromatography (silica gel, diethylether). Yield: 110 mg (41%) of a yellow oil; IR ν 3465-3445 (NH), 1626 (CN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 10.11 (br s, 1H, NH), 8.68 (dd, 1H, J_{46} = 1.6 Hz, J_{56} = 4.4 Hz, pyridazine H-6), 7.45 (dd, 1H, J_{45} = 9.1 Hz, J_{56} = 4.4 Hz, pyridazine H-5), 7.05 (dd, 1H, J_{45} = 9.1 Hz, J_{46} = 1.6 Hz, pyridazine H-4), 4.36 (q, 2H, J = 7.0 Hz, CH_2), 1.36 [s, 9H, $C(CH_3)_3$], 1.30 (t, 3H, J = 7.0 Hz, CH_3); ^{1}H-NMR ($CDCl_3$): δ 10.16 (br s, 1H, NH), 8.63 (dd, 1H, J_{46} = 1.5 Hz, J_{56} = 4.4 Hz, pyridazine H-6), 7.24 (dd, 1H, J_{45} = 8.9 Hz, J_{56} = 4.4 Hz, pyridazine H-5), 7.04 (dd, 1H, J_{45} = 8.9 Hz, J_{46} = 1.5 Hz, pyridazine H-4), 4.43 (q, 2H, J = 7.1 Hz, CH_2), 1.42 [s, 9H, $C(CH_3)_3$], 1.37 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C-NMR ($CDCl_3$): δ 163.3 (pyridazine C-3), 157.0 (C=N), 145.1 (pyridazine C-6), 127.1, 125.7 (pyridazine C-4, pyridazine C-5), 62.3 (CH_2), 51.3 [*C*$(CH_3)_3$], 29.8 [C(*C*$H_3)_3$], 14.5 (CH_3); MS *m/z* % 222.1 (M^+, 75).

Anal. Calcd for $C_{11}H_{18}N_4O$: C, 59.44; H, 8.16; N, 25.20; Found: C, 59,84; H, 7.82; N, 24.95.

N-(1,1-Dimethylethyl)-*O*-phenyl-*N'*-(2-pyrazinyl)isourea (**4cb**).

Phenol (80 mg, 0.85 mmol) and catalytic amounts of copper(II)chloride were added to a solution of 1,1-dimethylethyl-pyrazine-2yl-carbodiimide (**1c**) (100 mg, 0.57 mmol) in 5 mL of 1,4-dioxane and the mixture was stirred for 2 hours at room temperature. The solvent was removed *in vacuo* and the remaining residue was purified by column chromatography (silica gel, dichloromethane/ethyl acetate, 19:1) followed by recrystallisation from ethanol/water. Yield: 124 mg (80%) of colorless crystals, mp 86-92 °C; IR ν 3569-3414 (NH), 1622 (CN) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 9.70 (br s, 1H, NH), 8.19 (dd, 1H, J_{36} = 1.5 Hz, J_{56} = 2.9 Hz, pyrazine H-6), 8.02 (d, 1H, J_{56} = 2.9 Hz, pyrazine H-5), 7.90 (d, 1H, J_{36} = 1.5 Hz, pyrazine H-3), 7.45-7.37 (m, 2H, phenyl H-3/5), 7.26-7.15 (m, 3H, phenyl H-2/6, phenyl H-4), 1.47 [s, 9H, C(CH_3)$_3$]; ^{1}H-NMR ($CDCl_3$): δ 9.87 (br s, 1H, NH), 8.09 (d, 1H, J_{36} = 1.5 Hz, pyrazine H-3), 8.06 (dd, 1H, J_{36} = 1.5 Hz, J_{56} = 2.7 Hz, pyrazine H-6), 7.96 (d, 1H, J_{56} = 2.7 Hz, pyrazine H-5), 7.44-7.36 (m, 2H, phenyl H-3/5), 7.26-7.16 (m, 3H, phenyl H-2/6, phenyl H-4), 1.52 [s, 9H, C(CH_3)$_3$]; ^{13}C-NMR ($CDCl_3$): δ 157.3, 156.7 (pyrazine C-2, C=N), 152.1 (phenyl C-1), 144.7, 139.1, 135.5 (pyrazine C-3, pyrazine C-5, pyrazine C-6), 129.1 (phenyl C-3/5), 124.9 (phenyl C-4), 121.9 (phenyl C-2/6), 51.9 [*C*(CH_3)$_3$], 30.0 [C(*C*H_3)$_3$]; MS *m/z* % 270.1 (M^+, 59).

Anal. Calcd for $C_{15}H_{18}N_4O$: C, 66.65; H, 6.71; N, 20.72; Found: C, 66.88; H, 6.65; N, 20.58.

X-Ray Structure Determinations of **3aa** and **2cf**.

Crystal Data of **3aa**.

$C_{15}H_{19}N_5S$, M_r = 301.41, orthorhombic, space group Pbca (no. 61), a = 11.645(6) Å, b = 16.198(8) Å, c = 17.946(8) Å, V = 3385(3) Å^3, Z = 8, D_x = 1.183 Mg/m^{-3}, λ(Mo-Kα) = 0.71073 Å, μ = 0.192 mm^{-1}, T = 297(2) K. A yellow prism of 0.70 x 0.42 x 0.36 mm was used for X-ray data collection with a Bruker SMART CCD area detector three-circle diffractometer and graphite monochromatized Mo Kα radiation. The intensities of 37809 reflections with θ < 27.0° were measured by ω-scan frames, corrected for *LP* and absorption, and were merged to 3646 unique reflections, R_{int} = 0.049. The structure was solved with direct methods and was refined on F^2 using program SHELXL97 [16]. All non-hydrogen atoms were refined anisotropically. N-bound hydrogen atoms fully refined, C-bound hydrogen atoms inserted in calculated positions. The final least-squares refinement varied 203 parameters and converged at $R1$ = $\Sigma||F_o|-|F_c||/\Sigma|F_o|$ = 0.052, $wR2$ = $[\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2}$ = 0.118, and S = 1.04 for all 3646 unique reflections; $R1$ = 0.038 for the 2840 observed data [$I>2\sigma(I)$].

A view of the molecular structure is shown in Figure 1b with selected geometric data in the figure caption. The three N-bonded hydrogen atoms show very diverse hydrogen bond interactions: N4-bound H4 is directed to the π-orbitals of the phenyl ring thus displaying a weak non-classical intramolecular H-bond; N5-bound H5a forms a strongly bent intramolecular H-bond to S [N5···S = 3.051 Å, N5-H5a···S = 113(2)°]; and N5-bound H5b exhibits a straight intermolecular hydrogen bond to N1 of a neighboring molecule (N5···N1 = 3.036 Å, N5-H5b···N1 = 173°).

Crystal Data of **2cf**.

$C_{16}H_{21}N_5$, M_r = 283.38, monoclinic, space group $P2_1/c$ (No. 14), a = 10.594(4) Å, b = 12.909(5) Å, c = 12.053(5) Å, β = 107.42(1)°, V = 1572.7(11) Å^3, Z = 4, D_x = 1.197 Mg/m^{-3}, λ(Mo-Kα) = 0.71073 Å, μ = 0.075 mm^{-1}, T = 297(2) K. A pale yellow prism of 0.66 x 0.22 x 0.18 mm was used for X-ray data collection under conditions specified above. 18615 reflections with θ < 27.0° were measured by ω-scan frames, corrected for *LP* and absorption and were merged to 3437 unique reflections, R_{int} = 0.025. Structure solution with direct methods, refinement on F^2 with anisotropic displacement params for all non-hydrogen atoms: N-bound hydrogen atom fully refined, C-bound H atoms inserted in calculated positions. The final refinement varied 195 parameters and converged at $R1$ = 0.047, $wR2$ = 0.101, and S = 1.03 for all data; $R1$ = 0.035 for the 2542 observed data [$I>2\sigma(I)$].

A view of the molecular structure is shown in Figure 2b with salient geometric data in the figure caption. The N-bound hydrogen atom H5n is pointing in a similar way to the phenyl ring as in compound **3aa** (Figure 1b), but the orientation of the ring is here less favorable for a non-classical hydrogen bond interaction because C5-N5-C11=121.8° is larger than C5-S-C10=101.7° in **3aa**. Nitrogen atoms like N1 or N2 are too far off from this H (>3 Å) to function as H-bond acceptors.

Complete crystallographic data for the two structures (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-171080 and 171081. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: +44 1223 336033, email: deposit@ccdc.cam.ac.uk).

Acknowledgement.

The authors are grateful to Univ.-Prof. Dr. W. Holzer (Institute of Pharmaceutical Chemistry, University of Vienna) for helpful discussions concerning the NOE experiments.

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