Synthesis and Reactivity of 2-Pyrrolidino-, 2-*N*-Methylpiperazino-, 2-Piperidino-, and 2-Morpholino-1,3,4-thiadiazines

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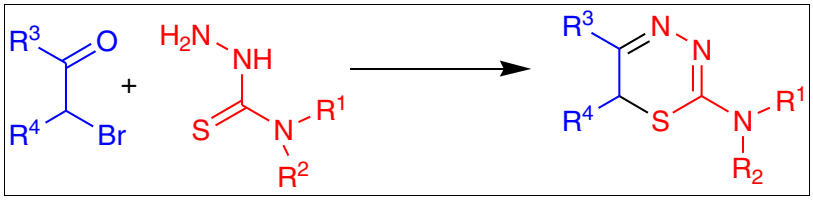

A variety of 2-pyrrolidino-, 2-*N*-methylpiperazino-, 2-piperidino-, and 2-morpholino-1,3,4-thiadiazines were prepared by cyclocondensation of phenacyl halides with thiosemicarbazides. Heating of the products resulted in desulfurization and formation of pyrazoles. The rate of this process strongly depends on the substitution pattern of the 1,3,4-thiadiazines.

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INTRODUCTION

1,3,4-Thiadiazines are of considerable biological and pharmacological relevance. 1,3,4-Thiadiazine derivatives have attracted considerable interest in medicinal chemistry because of their high pharmacological activity and low toxicity. Many 2-amino-1,3,4-thiadiazine derivatives have been shown to act as matrix metalloproteinase inhibitors [1,2]. 2-Alkylimino- and 2-alkyamino-1,3,4-thiadiazines are used as cardiotonic and spasmolytic agents [3–8]. In addition, it has been reported that 1,3,4-thiadiazin-2-ones act as cardiotonic with calcium sensitizing activity [9–11]. 3-Phenylazo-1*H*-4,2,1-thiadiazines are active against deficient bone growth [12]. 3-Nitrobenzyl-5-aryl-1,3,4-thiadiazin-2-ones and 1,3,4-thiadiazin-2-ones are phosphodiesterase IV inhibitors that can be used for the treatment of tumours and AIDS [13,14]. 2-Nitrosimino-3,6-dihydro-2*H*-1,3,4-thiadiazines [15], *N*-morpholinyl-, *N*-thiomorpholinyl-, and *N*-piperidinyl-1,3,4-thiadiazines [16] exhibit antithrombotic activities. 2-(*N*-Methylpiperazino)-1,3,4-thiadiazine dihydrobromides display antiarrhythmic activity [17]. Some 1,3,4-thiadiazin-2-ones can be used for the treatment of erectile dysfunction [18]. 1,3,4-Thiadiazines may be used in agricultural chemistry as herbicides [19], fungicides [20], insecticides [21], and plant-growth agents [22].

RESULTS AND DISCUSSION

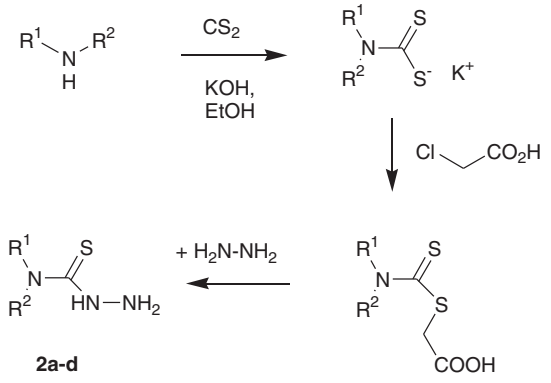
Dependent on the reaction conditions and substitution pattern, the cyclocondensation of α-haloketones with 4-alkylthiosemicarbazides can result in the formation of thiazolo-2-hydrazones, thiazolon-2-imides, or 1,3,4-thiadiazines. The latter may undergo desulfurization to give pyrazoles [23]. In contrast, the cyclocondensation of 4,4-dimethylthiosemicarbazides with α-haloketones can exclusively result in the formation of 1,3,4-thiadiazines, because of the double substituted amino group [24]. In our present study, we investigated the cyclization of novel 4,4-disubstituted thiosemicarbazides with α-haloketones. In this context, we were interested in the influence of the substitution pattern on the stability of the 1,3,4-thiadiazines. As novel building blocks, we chose, for the first time, pyrrolidino-thiocarbonyl-hydrazine (**2a**) and *N*-methyl-piperazino-thiocarbonyl-hydrazine (**2b**). Pyrrolidino-thiocarbonyl-hydrazine (**2a**) was prepared from *S*-(pyrrolidino-thiocarbonyl)-thioglycolic acid and hydrazine hydrate (100%) in an alkaline solution (heating for 1 h). *S*-(Pyrrolidino-thiocarbonyl)-thioglycolic acid was prepared from pyrrolidine and CS_2 and subsequent alkylation with chloroacetic acid. *N*-Methyl-piperazino-thiocarbonyl-hydrazine (**2b**) was prepared, in analogy to **2a**, from *S*-(*N*-methyl-piperazino-thiocarbonyl)-thioglycolic acid and hydrazine hydrate. *S*-(*N*-Methyl-piperazino-thiocarbonyl)-thioglycolic acid was prepared from *N*-methyl-piperazine, CS_2, and chloroacetic acid. Thiocarbonylhydrazines **2c,d** were previously mentioned in the literature, but without NMR-spectroscopic data. We have prepared these compounds in analogy to **2a,b** and provide a comprehensive characterization (Scheme 1).

The reaction of **2a–d** with α-bromo- and α-chloroacetophenones **1a–g** proceeded already by gentle heating of an EtOH solution of the starting materials to give 2-pyrrolidino-5-phenyl-6*H*-1,3,4-thiadiazines **3a–g**, 2-(*N*-methyl-piperazino)-5-phenyl-6*H*-1,3,4-thiadiazins **3h–m**, and the 2-piperidino- and 2-morpholino-5-(4-fluorophenyl)-1,3,4-thiadiazines **3o,p** in the form of their hydrochlorides and hydrobromides. Analogous products, that is, 2-

dimethylamino-, 2-piperidino-, and 2-morpholino-5-phenyl-6*H*-1,3,4-thiadiazines, have been previously reported [23,24]. To avoid desulfurization, it proved to be important to keep the reaction time short (5–10 min). The hydrobromides and hydrochlorides were purified by recrystallization from EtOH. The free bases **4a–f** and **4h–l** were obtained by addition of ammonia that was isolated as highly viscous oil that became solid upon standing (Scheme 2; Table 1).

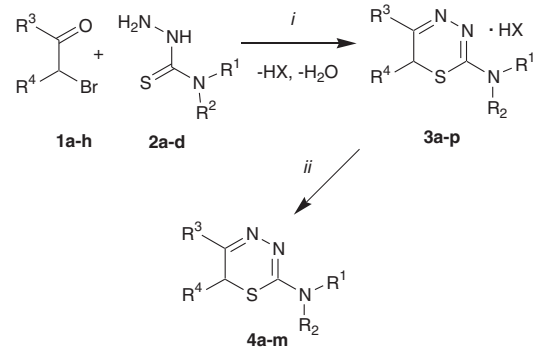
The NMR-spectroscopic data confirm the structures of 1,3,4-thiadiazines **3a–p** and **4a–m**. The presence of the 6-CH_2 signals confirms that the products reside in their 6*H* tautomeric form. The signals of the hydrogen halides **3a–m** and **3o,p** are observed in the range of 3.90 to 4.40 ppm (DMSO-d_6). In case of the free bases **4a–f** and **4h–m**, the values are in the range of 3.47 and 3.59 ppm ($CDCl_3$). To study the influence of a phenyl group located at position 6 on the stability of the 1,3,4-thiadiazine system, we carried out the cyclocondensation of 2-bromo-1,2-diphenylethan-1-one **1h** with pyrrolidino-thiocarbonyl-hydrazine (**2a**) and 1-methyl-piperazino-thiocarbonyl-hydrazine (**2b**). The starting materials were stirred for 1 h in dry ethanol, and subsequently, an aq. solution of sodium ethanolate was added. After heating for a short period of time and cooling, yellow crystals precipitated, that is, 2-pyrrolidino-5,6-diphenyl-6*H*-1,3,4-thiadiazine **4g** and 2-(*N*-methyl-piperazino)-5,6-diphenyl-6*H*-1,3,4-thiadiazine **4m**. Treatment of an ethanol solution of the free base **4m** with ethanolic hydrochloric acid yielded the hydrochloride **3n**. It proved to be important to keep the solution with a neutral pH during the addition of sodium ethanolate in order to avoid that the products undergo a base-mediated desulfurization and formation of pyrazoles. This type of transformation has been previously noted for several thiadiazines. In addition, the reaction time must be short, because prolonged heating also resulted in the formation of pyrazoles.

Scheme 1. Synthesis of thiocarbonylhydrazines (**2a–d**).



2a-d

Scheme 2. Synthesis of 1,3,4-thiadiazines **3a–p, 4a–m**: *conditions*: *i*, reflux, EtOH; *ii*, aq. ammonia.



1a-h **2a-d** **3a-p** **4a-m**

The reaction of **4a,b** with 4-nitrobenzaldehyde (p-NBA) afforded 6-(4-nitrobenzylidene)-1,3,4-thiadiazines **5a,b**. The reactions proceeded by aldol-type condensation of position 6 with the aldehyde. Analogous reactions of 2-dimethylamino-, 2-piperidino-, and 2-morpholino-5-phenyl-6*H*-1,3,4-thiadiazines have been previously reported [23,24]. The stability of products **5a,b** is remarkable, as, under identical conditions, 2-amino- and 2-alkyl(aryl)amino-5-phenyl-6*H*-1,3,4-thiadiazines are cleaved to give ω-(4-nitrobenzylidene)-acetophenone-semicarbazones [25]. These semicarbazones were hydrolyzed by hydrochloric acid to the corresponding semicarbazides and ω-(4-nitrobenzylidene)-acetophenones (Scheme 3).

Heating of 2-pyrrolidino-6*H*-1,3,4-thiadiazines **4a–c** with 2-(*N*-methyl-piperazino)-6*H*-1,3,4-thiadiazine **4i** in the presence of acetic anhydride resulted in the formation of 1-acetyl-3-pyrrolidino-4-acetylmercapto-5-aryl-pyrazoles **6a–c** and of 1-acetyl-3-(*N*-methylpyrrolidino)-4-acetylmercapto-5-(4-bromophenyl)-pyrazole **6d**. Their formation can be explained by ring transformation and acetylation. It has been previously reported that related products were prepared by reaction of acetic anhydride with 2-methylamino-, 2-dimethylamino-, 2-piperidino-, and morpholino-5-phenyl-6*H*-1,3,4-thiadiazines (Schemes 4 and 5) [23,24].

An overview of the reactions carried out by heating in conc. hydrochloric acid, dilute hydrochloric acid (2*M*), and dilute aq. NaOH (2*M*) is given in Table 2. In contrast to the reaction of 1-acetyl-3-acetylmethylamino-4-acetylmercapto-5-phenyl-pyrazole with conc. HCl, the analogous reactions of 1-acetyl-3-pyrrolidino-4-acetylmercapto-5-phenyl-pyrazoles **6a–c** afforded the sulfur-free 3-pyrrolidino-5-phenyl-pyrazoles **7a–c**. Disulfides were not formed. The basic hydrolysis of diacetyl-pyrazoles **6a–c** resulted in the formation of dipyrazolyl-(4,4′)-disulfides **8a–c**. Likewise, heating of acylated 3-piperidino-, 3-morpholino-, and 3-dimethylamino-5-aryl-pyrazoles in a 2*M* aq. solution of NaOH afforded disulfides **B** [23,24]. Disulfides **B** are also obtained when 2-methylamino- and 2-phenylamino-5-phenyl-1,3,4-thiadiazines were heated in toluene (Tables 3–6) [23].

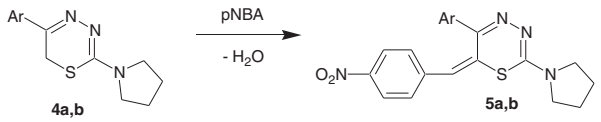
Table 1

Synthesis of hydrohalogenides of 1,3,4-thiadiazines **3a–p** and free bases of **4a–m**.

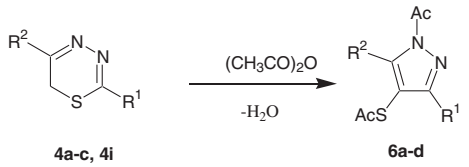
α-Haloketones	R^1	R^2	R^3	R^4		%[a] hydrobromide		%[a] free base
1a		$-(CH_2)_4-$	C_6H_5	H	**3a**	73	**4a**	75
1b		$-(CH_2)_4-$	4-BrC_6H_4	H	**3b**	72	**4b**	75
1c		$-(CH_2)_4-$	4-ClC_6H_4	H	**3c**	71	**4c**	69
1d		$-(CH_2)_4-$	4-FC_6H_4	H	**3d**	73	**4d**	72
1e		$-(CH_2)_4-$	4-$CH_3C_6H_4$	H	**3e**	78	**4e**	76
1f		$-(CH_2)_4-$	4-$CH_3OC_6H_4$	H	**3f**	74	–	–
1g		$-(CH_2)_4-$	4-$NO_2C_6H_4$	H	**3 g**	72	**4f**	69
1h		$-(CH_2)_4-$	C_6H_5	C_6H_5	–	–	**4g**	72
1a		$-(CH_2)_2-(NCH_3)-(CH_2)_2-$	C_6H_5	H	**3h**	68	**4h**	66
1b		$-(CH_2)_2-(NCH_3)-(CH_2)_2-$	4-BrC_6H_4	H	**3i**	75	**4i**	73
1c		$-(CH_2)_2-(NCH_3)-(CH_2)_2-$	4-ClC_6H_4	H	**3j**	70	**4j**	70
1d		$-(CH_2)_2-(NCH_3)-(CH_2)_2-$	4-FC_6H_4	H	**3 k**	79	–	–
1f		$-(CH_2)_2-(NCH_3)-(CH_2)_2-$	4-$(MeO)C_6H_4$	H	**3 l**	74	**4 k**	73
1g		$-(CH_2)_2-(NCH_3)-(CH_2)_2-$	4-$(O_2N)C_6H_4$	H	**3 m**	80	**4 l**	77
1h		$-(CH_2)_2-(NCH_3)-(CH_2)_2-$	C_6H_5	C_6H_5	**3n**	73 [b]	**4 m**	69
1d		$-(CH_2)_5-$	4-FC_6H_4	H	**3o**	72	–	–
1d		$-(CH_2)_2-O-CH_2)_2-$	4-FC_6H_4	H	**3p**	76	–	–

[a]Isolated yields.
[b]Isolated in the form of its hydrochloride.

Scheme 3. Synthesis of 2-pyrrolidino-5-aryl-(4-nitrophenylbenzylidene)-1,3,4-thiadiazines **5a,b**.



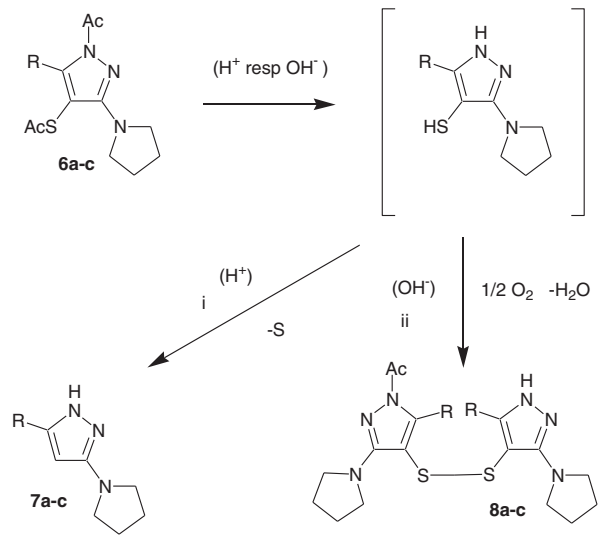
Scheme 4. Synthesis of 1-acetyl-4-acetylmethylthio-5-aryl-pyrazole **6a–d**.



Hydrolysis of acylated 3-piperidino-, 3-morpholino-, and 3-dimethylamino-5-aryl-pyrazoles in 2*M* HCl afforded the sulfur-free pyrazoles **A** in 62–64% yield. Disulfides **B** are formed in 20–24% yields. The use of conc. HCl did not result in a considerable change of the ratio of **A** and **B** [23,24]. 3-Methylamino-4-methylthio-5-phenyl-pyrazole, formed by acidic hydrolysis of 3-methylamino-5-phenyl-pyrazole, was less easily desulfurized. The use of 2*M* hydrochloric acid afforded exclusively disulfides **B**. Employment of conc. HCl gave a mixture of disulfides **B** (60%) and of sulfur-free pyrazoles **A** (35%) [24].

Heating of 1,3,4-thiadiazines in glacial acetic acid also resulted in desulfurization and formation of pyrazoles.

Scheme 5. Hydrolysis of 1-acetyl-4-acetylmethylthio-5-aryl-pyrazoles **6a–d**; *conditions*: i by **6a–c**, ii by **6a–c**.



7a, 8a: R = C_6H_5 **7b, 8b**: R = 4-BrC_6H_4 **7c, 8c**: R = 4-ClC_6H_4

Table 2

Synthesis of **5a,b**.

	Ar	Yield (%)[a]
5a	C_6H_5	73
5b	4-BrC_6H_4	71

[a]Isolated yields.

Table 3

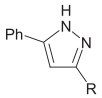
Synthesis of **6a–d**.

	R^1	R^2	Yield (%)[a]
6a		C_6H_5	64
6b		4-BrC_6H_4	69
6c		4-ClC_6H_4	67
6d		4-BrC_6H_4	71

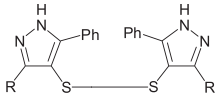
[a]Yields of isolated products.

Table 4

Synthesis of sulfur-free 5-phenyl-pyrazoles **A** and of disulfides **B**.



A



B

R	Conditions	Yield (%)[a]
	2*N* NaOH,15 min reflux Conc. HCl, 1 h reflux	**B (8a)** 70 **A (7a)** 71
	2*N* NaOH,15 min reflux 2*N* HCl, 30 min reflux	**B** 93 [23a] **A** 62 [23a] **B** 20 [23a]
	2*N* NaOH,15 min reflux 2*N* HCl, 30 min reflux	**B** 92 [23a] **A** 64 [23a] **B** 24 [23a]
NMe_2	2*N* NaOH,1 h reflux 2*N* HCl, 1 h reflux	**B** 96 [24] **A** 64 [24] **B** 23 [24]
NHMe	2*N* HCl, 1 h reflux Conc. HCl, 1 h reflux	**B** 91 [24] **A** 35 [24] **B** 60 [24]

[a]Isolated yield of product **A** or **B**.

The rate of desulfurization was particularly high in case of 5,6-diphenyl-6*H*-1,3,4-thiadiazines **4g** and **4m**. Although the isolation of these compounds was possible, they were rapidly transformed into pyrazoles **7g** and **9c** by heating in glacial acetic acid, respectively. Heating of 6-unsubstituted 2-pyrrolidino- and 2-(*N*-methylpiperazino)-5-aryl-6*H*-1,3,4-thiadiazines **3f** and **4a–d, 4f,i,j** and of 2-piperidino- and 2-morpholino-5-aryl-1,3,4-thiadiazines **3o,p** for 2 h in glacial acetic acid resulted in the formation of 3-pyrrolidino- and 2-*N*-methylpiperazino-5-aryl-pyrazoles **7a–f, 7h,i** and of 3-piperidino- and 3-morpholino-4-aryl-pyrazoles **9a,b**, respectively. Treatment of an ethanol solution of the free base of **7d,g, 9a,b** with ethanolic hydrochloric acid or hydrobromic acid (48%) yielded the hydrochlorides and hydrobromides, respectively. A completely different reaction was observed when 2-phenyl-, 2-benzyl-, and 2-methylthio-5-aryl-1,3,4-thiadiazines were heated in glacial acetic acid [23]. These compounds underwent a ring contraction to give 4-mercapto-5-aryl-pyrazoles [23]. Prolonged heating in glacial acetic acid did not result in desulfurization and formation of sulfur-free pyrazoles. Heating of the mercapto-pyrazoles in ethanol for 10–24 h resulted in the formation of disulfides. The reaction time was decreased to 30 min by addition of iodine (Scheme 6).

The stability of the 1,3,4-thiadiazines depends of the substituents located at positions 2, 5, and 6. The substituent located at position 6 has the highest influence on the rate of desulfurization.

The cyclocondensation of ethyl 2-chloro-acetoacetate **1i** with pyrrolidino-, piperidino-, and morpholino-thiocarbonylhydrazines **2a,c,d** resulted in direct formation of pyrazoles **10a–c** via the corresponding 1,3,4-thiadiazines that could not be isolated. Likewise, the reaction of morpholino-thiocarbonyl-hydrazine with 2-chloro-acetylacetone **1j** (EtOH, gentle heating) resulted in cyclization and subsequent desulfurization to give 3-morpholino-4-acetyl-5-methyl-pyrazole hydrochloride **10d** (Scheme 7).

In conclusion, we have reported the synthesis of a variety of novel 1,3,4-thiadiazines. The presence of a phenyl group located at position 5 has a stabilizing effect on the 1,3,4-thiadiazine moiety. The presence of an electron-withdrawing group located at position 6 and the presence of the twofold alkylated amino group result in a destabilization of the 1,3,4-thiadiazine moiety and desulfurization.

EXPERIMENTAL

General procedure for the synthesis of thiocarbonylhydrazines 2a–d. (a) Synthesis of thiocarbamoylthioacetic acids: A solution of 55 g (1 mole) of potassium hydroxide in 50 mL of water (for **2a**: 40 g sodium hydroxide) and of 1 mole of the secondary amine in 150 mL of ethanol was mixed with 76 g (1 mole) of carbon disulfide with ice cooling, keeping the temperature below 20°C. After 1 h, a solution of 95 g (1 mole) of chloroacetic acid in 300 mL water, neutralized with 56 g of sodium carbonate, was added, and the mixture was kept for about 12 h. The acid was isolated by addition of 70 mL of conc. hydrochloric acid to the filtrate.

(b) Synthesis of thiocarbonylhydrazine: A solution of 0.76 mole of thiocarbamoylthioacetic acid in 190 mL of 2*M* sodium hydroxide (**2b**: 2*M* potassium hydroxide) and of 50 mL of hydrazine hydrate was refluxed for 15 min. After cooling, the thiocarbonyl hydrazide crystallized, and the precipitate was filtered off.

Table 5

3-Pyrrolidino- and 3-*N*-methylpiperazino-5-aryl-pyrazoles **7a–i** and **9a–c**.

	R^1	R^2	R^3	Starting material	%[a] hydrochloride	%[a] free base
7a		C_6H_5	H	**4a**	–	73
7b		$4BrC_6H_5$	H	**4b**	–	71
7c		$4ClC_6H_5$	H	**4c**	–	76
7d		$4FC_6H_5$	H	**4d**	68[b]	–
7e		$4CH_3OC_6H_5$	H	**3f**	–	69
7f		$4NO_2C_6H_5$	H	**4f**	–	73
7g		C_6H_5	C_6H_5	**4g**	71[c]	71
7h		$4FC_6H_5$	H	**3**	–	73
7i		$4FC_6H_5$	H	**3p**	–	71
9a		$4BrC_6H_5$	H	**4i**	72[b]	–
9b		$4ClC_6H_5$	H	**4j**	72[b]	–
9c		C_6H_5	C_6H_5	**4m**	–	68

[a]Isolated yields.
[b]Addition of ethanolic HCl.
[c]Hydrobromide, addition of HBr (48%).

Pyrrolidino-thiocarbonyl-hydrazine (2a). *S-(Pyrrolidino-thiocarbonyl)-thioglycolic acid*: prepared from 71 g (1 mole) of pyrrolidine in 150 mL of ethanol and 76 g (1 mole) of carbon disulfide. Yield: 81.68 g (74%), colourless needles (EtOH), mp 180°C. *Pyrrolidino-thiocarbonyl-hydrazine*: 156 g (0.76 mole) *S*-(pyrrolidino-thiocarbonyl)-thioglycol acid in 190 mL of 2*M* sodium hydroxide solution and 50 mL of hydrazine hydrate was refluxed for 1 h; ir (KBr, cm^{-1}): 3201 (m), 3161 (m), 3137 (m), 2968 (m), 2949 (m), 2875 (m), 1557 (s), 1431 (s), 1368 (s), 1354 (m), 1289 (m); ^1H nmr (DMSO-d_6, 300 MHz): δ = 1.88 (s, 2H, NH_2), 3.78–3.41 (m, 8H, H-pyrrolidine), 8.54 (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 75 MHz): δ = 24.94 (CH_2), 49.62 (CH_2), 179.76 (C=S); ms (EI, 70 eV): *m/z* (%) = 28 (32), 41 (34), 55 (75), 73 (100), 86 (5), 97 (3), 102 (3), 113 (61), 128 (44), 145 (M^+, 77). *Anal*. Calcd. for $C_5H_{11}N_3S$ (145.23): C, 41.35; H, 7.63; N, 28.93. Found: C, 41.34; H, 7.61; N, 28.91.

N-Methyl-piperazino-thiocarbonyl-hydrazine (2b). *Synthesis of N-(Methyl-piperazino-thiocarbonyl)-thioglycolic acid*: prepared from 99.7 g (1 mole) of *N*-methyl-piperazine and 76 g (1 mole) of carbon disulfide. *N*-(Methyl-piperazino-thiocarbonyl)-thioglycolic acid was not isolated. The solution of *N*-(methyl-piperazino-thiocarbonyl)-thioglycolic acid was neutralized with HCl and then refluxed with 60 mL of hydrazine hydrate for 1 h. The reaction yielded the *N-methyl-piperazino-thiocarbonyl-hydrazine (**2b**)*. Yield: 123.73 g (71%), colourless lamella (EtOH), mp 139°C; ir (KBr, cm^{-1}): 3250 (m), 3214 (m), 3131 (m), 2929 (m), 1557 (m), 1428 (m), 1365 (m), 1298 (m), 1255 (m), 1222 (m), 1146 (m), 1002 (m); ^1H nmr (DMSO-d_6, 300 MHz): δ = 2.32 (s, 3H, Me),

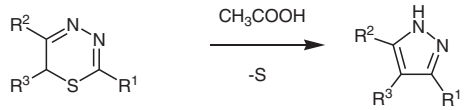
Table 6

Synthesis of 3-pyrrolidino-, 3-piperidino-, and 3-morpholino-4-ethoxycarbonyl- resp. 4-acetyl-pyrazoles **10a–d.**

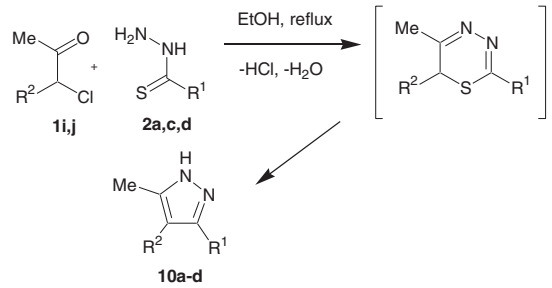
	R^1	R^2	mp (°C)	Yield (%)
10a		C_2H_5OCO	122	76
10b		C_2H_5OCO	159	77
10c		C_2H_5OCO	139	74
10d		CH_3CO	116	73

[a]Isolated yields.

Scheme 6. Synthesis of 3-pyrrolidino- and 3-(*N*-metylpiperazino)-5-aryl-pyrazoles **7a-i, 9a–c**.



Scheme 7. Synthesis of 3-pyrrolidino-, 3-piperidino-, and 3-morpholino-5-aryl-pyrazoles **10a–d**.



2.44–2.47 (t, 4H, 2xN-CH_2), 3.80–3.83 (t, 4H, 2xN-CH_2), 7.28 (s, 1H, NH); ms (El, 70 eV): *m/z* (%) = 42 (75), 59 (38), 71 (89), 99 (9), 128 (10), 143 (24), 174 (M^+, 100), 192 (4). *Anal*. Calcd. for $C_6H_{14}N_4S$ (174.27): C, 41.35; H, 8.10; N, 32.15. Found: C, 41.39; H, 8.12; N, 32.10.

Piperidino-thiocarbonyl-hydrazine (2c). *S-(Piperidino-thiocarbonyl)-thioglycolic acid*: prepared from 87 g (1 mole) of piperidine and 76 g (1 mole) of carbon disulfide. *Piperidino-thiocarbonyl-hydrazine*: prepared from 166 g (0.76 mole) of *S*-(piperidino-thiocarbonyl)-thioglycolic acid in 190 mL of 2*M* sodium hydroxide solution and 50 mL of hydrazine hydrate. Yield: 95.61 g (79%), colourless lamella (EtOH), mp 94°C; ir (KBr, cm^{-1}): 3199 (m), 3165 (m), 2931 (m), 2853 (m), 1550 (m), 1512 (m), 1428 (m), 1363 (m), 1252 (m), 1219 (m), 1001 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.59–1.75 (m, 6H, 3xCH_2), 3.54–3.60 (t, 4H, 2xN-CH_2), 4.90 (s, br, 2H, NH_2), 9.21 (s, 1H, NH); ms (El, 70 eV): *m/z* (%) = 28 (53), 41 (81), 56 (54), 70 (61), 84 (100), 96 (8), 113 (6), 128 (49), 142 (32), 159 (M^+, 71). *Anal*. Calcd. for $C_6H_{13}N_3S$ (159.25): C, 45.25; H, 8.23; N, 26.39. Found: C, 45.25; H, 8.24; N, 26.39.

Morpholino-thiocarbonyl-hydrazine (2d). *S-(Morpholino-thiocarbonyl)-thioglycolic acid*: prepared from 87 g (1 mole) of morpholine, 68 g (0.76 mole), and 76 g (1 mole) of carbon disulfide. *Morpholino-thiocarbonyl-hydrazine*: prepared from *S*-(morpholino-thiocarbonyl)-thioglycolic acid in 190 mL of 2*M* sodium hydroxide solution and 50 mL of hydrazine hydrate (reflux, 15 min). Yield: 109.06 g (89%), colourless needles (H_2O), mp 176°C; ir (KBr, cm^{-1}): 3263 (s), 3217 (s), 3139 (s), 3038 (m), 2894 (m), 2865 (m), 1548 (s), 1423 (s), 1384 (s), 1359 (s), 1299 (m), 1278 (s), 1228 (s), 1205 (s), 1122 (s), 1049 (m), 1016 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 3.55–3.58 (m, 4H, 2xCH_2), 3.68–3.70 (m, 4H, 2xCH_2), 4.81 (s, 2H, NH_2), 9.12 (s, br, 1H, NH); ms (El, 70 eV): *m/z* (%) = 28 (31), 45 (16), 61 (25), 73 (7), 86 (100), 117 (2), 130 (47), 144 (18), 161 (M^+, 82). *Anal*. Calcd. for $C_5H_{11}N_3OS$ (161.23): C, 37.25; H, 6.88; N, 26.06. Found: C, 37.22; H, 6.86; N, 26.01.

General procedure for the synthesis of 3a–m, 3o,p and 4a–f, 4h–l. An ethanol solution (15 mL) of 10 mmol of **1a–d** and of 10 mmol of phenacylbromides or phenacylchlorides was refluxed for 10 min. The hot solution was filtered, and the filtrate was cooled and slowly added to ether (400 mL) with stirring and scratching the glass surface. A precipitate formed. In some cases, the precipitate already formed when the reaction mixture was cooled. The solid was filtered off, washed with ether/EtOH (9:1) and recrystallized. *Free bases*: To an EtOH solution of the hydrobromide was added a dilute aqueous solution of ammonia until pH = 8 was reached. A precipitate formed that was filtered off and recrystallized from EtOH.

2-Pyrrolidino-5-phenyl-6H-1,3,4-thiadiazine. **Hydrobromide 3a**: prepared from 1.45 g (10 mmol) of **2a** and 1.99 g (10 mmol) of phenacylbromide **1a**. Yield: 2.38 g (73%), colourless prisms (EtOH), mp.: 218°C; ir (KBr, cm^{-1}): 3406 (m), 2979 (m), 2877 (m), 2826 (m), 1614 (m), 1586 (s), 1449 (m), 1316 (m), 776 (m), 694 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 2.04 (m, 4H, 2xCH_2), 3.71–3.75 (t, 4H, 2xN-CH_2), 4.36 (s, 2H, 6-CH_2, thiadiazine), 7.54–7.96 (m, 5H, ArH); ^{13}C nmr (DMSO-d_6, 75 MHz): δ = 22.30 (6-CH_2, thiadiazine) 24.79 (CH_2), 53.1 (CH_2), 124 (ArH), 126.40 (ArH), 139.40 (Ar), 148.46 (Ar), 149.0 (5-C, thiadiazine), 158 (2-C, thiadiazine); ms (EI, 70 eV): *m/z* (%) = 28 (14), 55 (24), 73 (51), 113 (100), 116 (2), 147 (1), 216 (6), 245 (M^+, 58). *Anal*. Calcd. for $C_{13}H_{16}BrN_3S$ (326,26): C, 47.86; H, 4.94; N, 12.88. Found: C, 47.75; H, 4.76; N, 12.73. **Free base 4a**: Yield: 1.84 g (75%), yellow prisms (EtOH), mp 112°C; ir (KBr, cm^{-1}): 2970 (m), 2871 (m), 1509 (s), 1483 (s), 1473 (m), 1459 (s), 1449 (m), 1396 (m), 1368 (m), 1362 (m), 1323 (m), 1190 (m), 914 (m), 761 (m), 697 (m), 588 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.96–2.01 (m, 4H, 2xCH_2), 3.56–3.68 (s, 2H, 6-CH_2, thiadiazine), 3.64–3.68 (t, 4H, 2xN-CH_2), 7.38–7.91 (m, 5H, ArH); ^{13}C nmr ($CDCl_3$, 75 MHz): δ = 21.60 (6-CH_2, thiadiazine) 24.93 (CH_2), 48.08 (CH_2), 126.31 (ArH), 128.48 (ArH), 129.15 (Ar), 136.10 (Ar), 145.26 (5-C, thiadiazine), 148.42 (2-C, thiadiazine); ms (EI, 70 eV): *m/z* (%) = 28 (9), 55 (32), 731 (47), 113 (100), 115 (5), 146 (3), 184 (1), 185 (1), 216 (7), 245 (M^+, 41). *Anal*. Calcd. for $C_{13}H_{15}N_3S$ (245, 34): C, 63.64; H, 6.16; N, 17.13. Found: C, 63.43; H, 5.81; N, 16.94.

2-Pyrrolidino-5-(4-bromophenyl)-6H-1,3,4-thiadiazine. **Hydrobromide 3b**: prepared from 1.45 g (10 mmol) of **2a** and 2.78 g (10 mmol) of 4-bromo-phenacylbromide **1b**. Yield: 2.92 g (72%), yellow prisms (EtOH), mp 129°C; ir (KBr, cm^{-1}): 3093 (m), 3050 (m), 2972 (m), 2843 (m), 1619 (m), 1584 (s), 1448 (m), 1412 (m), 1317 (m), 852 (m), 811 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 2.04 (m, 4H, 2xCH_2), 3.41–3.45 (t, 4H, 2xN-CH_2), 4.31 (s, 2H, 6-CH_2, thiadiazine), 7.64–7.88 (m, 4H, ArH), 13.00 (s, 1H, NH^+); ^{13}C nmr (DMSO-d_6, 75 MHz): δ = 27.18, 125.34 (ArH), 129.12 (ArH), 132.38 (Ar), 149.37 (5-C, thiadiazine), 158.84 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (49), 73 (39), 102 (15), 113 (100), 141 (2), 183 (2), 279 (4), 323/325 (M^+, 10/10). *Anal*. Calcd. for $C_{13}H_{15}Br_2N_3S$ (405.15): C, 38.54 H, 3.73 N, 10.37. Found: C, 38.87, H, 3.98 N, 10.27. **Free base 4b**: Yield: 2.43 g (75%), yellow prisms (EtOH), mp 157°C; ir (KBr, cm^{-1}): 2968 (m), 2868 (m), 1586 (m), 1531 (m), 1502 (s), 1482 (s), 1457 (m), 1409 (m), 1368 (m), 1330 (m), 1069 (m), 1002 (m), 915 (m), 943 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.96–2.00 (m, 4H, 2xCH_2), 3.52 (s, 2H, 6-CH_2), 3.63–3.68 (t, 4H, 2xN-CH_2), 7.52–7.77 (m, 4H, ArH); ms (El, 70 eV): *m/z* (%) = 28 (23), 55 (46), 102 (21), 113 (100), 142 (2), 183 (7), 293 (1), 323/325 (M^+, 15/16). *Anal*. Calcd. for $C_{13}H_{14}BrN_3S$ (324,24): C, 48.16; H, 4.35; N, 12.96. Found: C, 48.42; H, 4.56; N, 13.06.

2-Pyrrolidino-5-(4-chlorophenyl)-6H-1,3,4-thiadiazine. **Hydrobromide 3c**: prepared from 1.45 g (10 mmol) **2a** and 1.89 g (10 mmol) of 4-chloro-phenacylbromide **1c**. Yield: 2.56 g (71%), yellow prisms (EtOH), mp 223°C; ir (KBr, cm^{-1}): 3050 (m), 2973 (m), 2841 (m), 1620 (m), 1584 (s), 1449 (m), 1413 (m), 1317 (m), 1093 (m), 854 (m), 815 (m), 707 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 2.04 (m, 4H, 2xCH_2), 3.70–3.74 (t, 4H, 2xN-CH_2), 4.31 (s, 2H, 6-CH_2, thiadiazine), 7.64–7.95 (m, 4H, ArH), 13.02 (s, 1H, NH^+); ms (El, 70 eV): *m/z* (%) = 41 (24), 55 (32), 73 (47), 113 (100), 137 (8), 148 (5), 193 (1), 250 (3), 279 (M^+, 28). *Anal*. Calcd. for $C_{13}H_{15}BrClN_3S$ (360.70): C, 43.29 H, 4.19 N, 11.65. Found: C, 43.53 H,4.29,N, 11.63. **Free base 4c**: Yield: 1.93 g (69%), yellow prisms (EtOH), mp 139°C; ir (KBr, cm^{-1}): 2967 (m), 2874 (m), 1536 (m), 1507 (s), 1473 (s), 1454 (s), 1412 (m), 1366 (s), 1325 (m), 1218 (m), 1191 (m), 1089 (m), 915 (m), 836 (m), 812 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.96–2.01 (m, 4H, 2xCH_2), 3.52 (s, 2H, 6-CH_2, thiadiazine), 3.63–3.68 (t, 4H, 2xN-CH_2), 7.37–7.84 (m, 4H, ArH); ^{13}C nmr ($CDCl_3$, 75 MHz): δ = 21.48 (6-CH_2, thiadiazine) 25.01 (CH_2), 48.21 (CH_2), 127.59 (ArH), 134.66 (ArH), 135.66 (Ar), 144.19 (5-C, thiadiazine), 148.51 (2-C, thiadiazine); ms (El, 70er): *m/z* (%) = 28 (7), 55 (26), 73 (48), 113 (100), 137 (9), 139 (3), 181 (1), 250 (3), 279 (M^+, 26). *Anal*. Calcd. for $C_{13}H_{14}ClN_3S$ (279.79): C, 55.81; H, 5.04; N, 15.02. Found: C, 55.92; H, 5.03; N, 14.97.

2-Pyrrolidino-5-(4-fluorophenyl)-6H-1,3,4-thiadiazine. **Hydrobromide 3d**: prepared from 1.45 g (10 mmol) of **2a** and 2.17 g (10 mmol) of 4-fluoro-phenacylbromide **1d**. Yield: 2.51 g (73%), yellow prisms (EtOH), mp 224°C; ir (RBr, cm^{-1}): 3038 (m), 2978 (m), 2833 (m), 1621 (m), 1595 (s), 1513 (m), 1449 (m), 1416 (m), 1320 (m), 1232 (m), 1158 (m), 854 (m), 812 (m), 735 (m), 577 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 2.04 (m, 4H, 2xCH_2), 3.38–3.45 (t, 4H, 2xN-CH_2), 4.30 (s, 2H, 6-CH_2, thiadiazine), 7.39–8.00 (m, 4H, ArH), 12.93 (s, 1H, NH^+); ms (El, 70 eV): *m/z* (%) = 51 (6), 76 (13), 102 (35), 137 (17), 160 (21), 187 (51), 290 (3), 325 (M^+, 100). *Anal*. Calcd. for $C_{15}H_{15}BrFN_3S$ (344.25): C, 45.36; H, 4.39; N, 12.21. Found: C, 45.29; H, 4.37; N, 12.20. **Free base 4d**: Yield: 1.89 g (72%), colourless prisms (EtOH), mp 214°C. IR (KBr, cm^{-1}): 2986 (m), 2872 (m), 1597 (m), 1505 (s), 1484 (5), 1458 (s), 1371 (m), 1319 (m), 1222 (m), 1170 (m), 1156 (m), 918 (m), 841 (m), 572 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.96–2.00 (m, 4H, 2xCH_2), 3.53 (s, 2H, 6-CH_2, thiadiazine), 3.63–3.68 (t, 4H, 2xN-CH_2), 7.07–7.89 (m, 4H, ArH); ^{13}C nmr ($CDCl_3$, 50 MHz): δ = 21.58 (6-CH_2, thiadiazine), 24.92 (2xCH_2), 48.16 (2xCH_2), 115.75 (d, J(C,F) = 21.2, ArH), 128.24 (d, J(C,F) = 8.1, ArH), 132.26 (d, J(C,F) = 3.3, Ar), 148.51 (5-C, thiadiazine), 160.898(d, J(C, F) = 247.3, Ar), 165.85 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 41 (1), 55 (14), 73 (29), 113 (100), 121 (16), 141 (4), 165 (2), 203 (3), 230 (6), 231 (9), 263 (M^+, 17). *Anal*. Calcd. for $C_{13}H_{14}FN_3S$ (263.33): C, 59.29; H, 5.36; N, 15.96. Found: C, 59.12; H, 5.32; N, 15.91.

2-Pyrrolidino-5-(4-tolyl)-6H-1,3,4-thiadiazine. **Hydrochloride 3e**: prepared from 1.45 g (10 mmol) **2a** and 2.13 g (10 mmol) of 4-methyl-phenacylbromide **1e**. Yield: 2.3 g (78%), yellow prisms (EtOH), mp 175°C; ir (KBr, cm^{-1}): 3036 (m), 2969 (s), 2875 (m), 2813 (s), 1584 (s), 1447 (m), 1413 (m), 1324 (m), 1183 (m), 1153 (m), 915 (m), 807 (m), 742 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 2.04 (s, 3H, Me), 2.46–2.52 (m, 4H, 2xCH_2), 3.70–3.74 (t, 4H, 2xN-CH_2), 4.31 (s, 2H, 6-CH_2, thiadiazine) 7.36–7.84 (m, 4H, ArH), 12.92 (s, 1H, NH^+); ms (El, 70 eV): *m/z* (%) = 36 (53), 55 (22), 73 (42), 113 (100), 117 (16), 161 (4), 162 (1), 230 (6), 259 (M^+, 72). *Anal*. Calcd. for $C_{14}H_{18}Cl\ N_3S$ (295,83): C, 56.84; H, 6.13; N, 14.20. Found: C, 52.43; H, 5.62; N, 10.84. **Free base 4e**: Yield: 1.97 g (76%), yellow prisms (EtOH), mp. 142°C; ir (KBr, cm^{-1}): 3030 (m), 2966 (m), 2921 (m), 2874 (m), 1503 (s), 1474 (s), 1455 (s), 1416 (m), 1366 (s), 1322 (s), 1226 (m), 1193 (m), 913 (m), 815 (m), 574 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.95–1.99 (m, 4H, 2xCH_2), 2.38 (s, 3H, Me), 3.53 (s, 2H, 6-CH_2, thiadiazine), 3.60–3.67 (t, 4H, 2xN-CH_2), 7.77–7.80 (m, 4H, ArH); ^{13}C nmr (DMSO-d_6, 50 MHz) δ = 21.22 (Me), 21.58 (6-CH_2, thiadiazine), 24.92 (2xCH_2), 48.05 (2xCH_2), 126.22 (ArH), 129.19 (ArH), 133.21 (Ar), 139.27 (Ar), 145.29 (5-C, thiadiazine), 148.37 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (42), 55 (25), 73 (41), 113 (100), 117 (15), 161 (3), 230 (5), 259 (M^+, 79). *Anal*. Calcd. for $C_{14}H_{17}N_3S$ (259.37): C, 64.83; H, 6.61; N, 16.20. Found: C, 64.53; H, 6.59; N, 16.18.

2-Pyrrolidino-5-(4-methoxyphenyl)-6H-1,3,4-thiadiazine. **Hydrochloride 3f**: prepared from 1.45 g (10 mmol) of **2a** and 2.29 g (10 mmol) of *p*-methoxy-phenacylbromide **1f**. Yield: 2.30 g (74%), yellow prisms (EtOH), mp 171°C; ir (KBr, cm^{-1}): 3419 (m), 2978 (m), 2836 (m), 1603 (s), 1582 (s), 1514 (m), 1460 (m), 1447 (m), 1424 (m), 1315 (s), 1255 (s), 1181 (m), 1009 (m), 847 (m), 587 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 2.03 (m, 4H, 2xCH_2), 3.73 (t, 4H, 2xN-CH_2), 3.85 (s, 3H, MeO), 4.29 (s, 2H, 6-CH_2, thiadiazine), 7.10–7.91 (m, 4H, ArH), 13.12 (s, 1H, NH^+); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 22.16 (6-CH_2, thiadiazine), 24.61 (2xCH_2), 51.19 (2xCH_2), 114.39 (ArH), 125.07 (Ar), 128.67 (ArH), 150.21 (5-C, thiadiazine), 158.58 (2-C, thiadiazine), 161.74 (OAr); ms (El, 70 eV): *m/z* (%) = 28 (7), 55 (23), 73 (47), 113 (100), 133 (49), 177 (4), 215 (1), 243 (6), 275 (M^+, 57). *Anal*. Calcd. for $C_{14}H_{18}ClN_3OS$ (311,83): C, 53.92; H, 5.82; N, 13.48. Found: C, 53.79; H, 5.81; N, 13.47.

2-Pyrrolidino-5-(4-nitrophenyl)-6H-1,3,4-thiadiazine. **Hydrobromide 3g**: prepared from 1.45 g (10 mmol) of **2a** and 2.44 g (10 mmol) of *p*-nitro-phenacylbromide **1g**. Yield: 2.67 g (72%), yellow prisms (EtOH), mp 211°C; ir (KBr, cm^{-1}): 2974 (m), 2822 (m), 1620 (m), 1598 (m), 1575 (s), 1521 (s), 1449 (m), 1415 (m), 1348 (s), 1313 (m), 860 (m), 751 (m); ^{1}H nmr

(DMSO-d_6, 300 MHz): δ = 2.05 (m, 4H, 2xCH$_2$), 3.39–3.75 (t, 4H, 2xN-CH$_2$), 4.39 (s, 2H, 6-CH$_2$, thiadiazine), 8.15–8.42 (m, 4H, ArH), 13.1 (s, 1H, NH$^+$); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 22.19 (6-CH$_2$, thiadiazine) 24.34 (CH$_2$), 51.22 (CH$_2$), 123.99 (ArH), 127.97 (ArH), 138.90 (Ar), 148.10 (Ar), 148.56 (5-C, thiadiazine), 158.29 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (43), 55 (24), 73 (48), 113 (100), 118 (3), 141 (1), 191 (4), 260 (4), 290 (M$^+$, 31). *Anal.* Calcd. for $C_{13}H_{15}BrN_4O_2S$ (371,25): C, 42.06; H, 4.07; N, 15.09. Found: C, 42.99; H, 4.27; N, 14.67. **Free base 4f**: Yield: 2,0 g (69%), yellow prisms (EtOH), mp 164°C; ir (KBr, cm^{-1}): 1598 (m), 1497 (s), 1456 (s), 1410 (m), 1367 (m), 1340 (s), 1319 (m), 1222 (m), 1191 (m), 917 (m), 857 (m); ^{1}H nmr (CDCl$_3$, 300 MHz): δ = 1.99–2.03 (m. 4H, 2xCH$_2$), 3.59 (s, 2H, 6-CH$_2$, thiadiazine), 3.65–3.69 (t, 4H, 2xN-CH$_2$), 8.02–8.24 (m, 4H, ArH); ^{13}C nmr(CDCl$_3$, 50 MHz): δ = 21.10 (6-CH$_2$, thiadiazine), 24.88 (2xCH$_2$), 48.31 (2xCH$_2$), 123.75 (ArH), 126.75 (ArH), 142.14 (Ar), 142.74 (Ar), 147.70 (5-C, thiadiazine), 148.72 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (71), 55 (49), 73 (62), 113 (100), 115 (8), 141 (4), 183 (5), 185 (4), 261 (2), 290 (M$^+$, 17). *Anal*. Calcd. for $C_{13}H_{14}N_4O_2S$ (290.34): C, 53.78; H, 4.86; N, 19.30. Found: C, 53.71; H, 4.85; N, 19.32.

2-Pyrrolidino-5,6-diphenyl-6H-1,3,4-thiadiazine. **Free base 4g**: 1.45 g (10 mmol) of **2a** and 2.75 g (10 mmol) of 2-bromo-1,2-diphenyl- ethan-1-one **1h** in ethanol were stirred at 20°C for 1 h. A sodium ethanolate solution (0.23 g; 10 mmol sodium and 10 mL of ethanol) was added. The solution was refluxed for 5 min. After cooling, the mixture was poured into ice water. Scratching of the flask resulted in crystallization of the products. Yield: 2.31 g (72%), yellow prisms (EtOH), mp 159°C; ir (KBr, cm^{-1}): 2970 (m), 2950 (m), 1501 (s), 1477 (s), 1457 (m), 1367 (m), 1320 (m), 1191 (m), 918 (m), 764 (m), 725 (m), 694 (m), 600 (m); ^{1}H nmr (CDCl$_3$, 300 MHz): δ = 1.87–1.94 (m, 4H, 2xCH$_2$), 3.60–3.65 (t, 4H, 2xN-CH$_2$), 5.17 (s, 1H, 6-CH, thiadiazine), 8.02–8.24 (m, 10H, 2xArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 24.75 (2xCH$_2$), 37.86 (6-CH$_2$, thiadiazine), 47.73 (2xCH$_2$), 126.14 (ArH), 127.46 (ArH), 127.90 (ArH), 128.46 (ArH), 128.75 (ArH), 129.09 (ArH) 136.67 (Ar), 137.18 (Ar), 144.64 (5-C, thiadiazine), 145.45 (2-C, thiadiazine); ms (El, 70 eV): *m/z* = 28 (40), 73 (39), 105 (3), 113 (100), 151 (2), 178 (20), 191 (3), 223 (15), 260 (8), 289 (41), 321 (M$^+$, 27), 329 (1). *Anal*. Calcd. for $C_{19}H_{19}N_3S$ (321.44): C, 70.99; H, 5.96; N, 13.07. Found: C, 70.89; H, 5.94; N, 12.98.

2-(N-Methyl-piperazino)-5-phenyl-6H-1,3,4-thiadiazine. **Hydrobromide 3h**: prepared from 1.74 g (10 mmol) of **2b** and 1.99 g (10 mmol) of phenacylbromide **1a**. Yield: 2.41 g (68%), yellow prisms (EtOH), mp.: 176°C; ir (KBr, cm^{-1}): 3129 (m), 3025 (m), 3003 (m), 2939 (m), 2657 (m), 2592 (m), 2475 (m), 1496 (s), 1466 (m), 1446 (m), 1422 (m), 1399 (s), 1367 (m), 1244 (m), 974 (m), 692 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 2.82 (s, 3H, Me), 3.28–3.41 (t, 4H, 2xN-CH$_2$), 3.75–3.79 (t, 4H, 2xN-CH$_2$) 4.40 (s, 2H, 6-CH$_2$, thiadiazine), 7.46–7.96 (m, 5H, -ArH), 10.85 (s, 1H, NH$^+$); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 21.69 (6-CH$_2$, thiadiazine), 42.17 (Me), 44.10 (CH$_2$), 51.77 (CH$_2$), 126.66 (ArH), 128.56 (ArH), 129.70 (ArH), 135.18 (Ar), 148.18 (5-C, thiadiazine), 150.95 (2-C, thiadiazine); ms (El, 70 eV): *m/z* = 28 (50), 56 (18), 71 (100), 103 (26), 124 (5), 143 (19), 172 (10), 204 (66), 217 (50), 242 (9), 274 (M$^+$, 19). *Anal*. Calcd. for $C_{14}H_{19}BrN_4S$ (355.30): C, 47.33; H, 5.39; N, 15.77. Found: C, 47.33; H, 5.38; N, 15.72. **Free base 4h**: Yield: 1.81 g (66%), yellow prisms (EtOH), mp 100°C; ir (KBr, cm^{-1}): 2935 (m), 2790 (m), 1488 (m), 1453 (m), 1372 (m), 1345 (m), 1289 (m), 1251 (m), 1230 (m), 1145 (m), 1003 (m), 699 (m); ^{1}H nmr (CDCl$_3$, 300 MHz): δ = 2.34 (s, 3H, Me), 2.48–2.52 (t, 4H, 2xN-CH$_2$), 3.56 (s, 2H, 6-CH$_2$), 3.79–3.82 (t, 4H, 2xN-CH$_2$), 7.41–7.91 (m, 5H, ArH); ms (El, 70 eV): *m/z* (%) = 42 (20), 59 (6), 71 (23), 104 (4), 143 (2), 172 (6), 204 (27), 217 (29), 242 (18), 274 (M$^+$, 100). *Anal*. Calcd. for $C_{14}H_{18}N_4$ S (274,39): C, 61.28; H, 6.61; N, 20.42. Found: C, 61.30; H, 6.60; N, 20.45.

2-(N-Methyl-piperazino)-5-(4-bromophenyl)-6H-1,3,4-thiadiazine. **Hydrobromide 3i**: prepared from 1.74 g (10 mmol) of **2b** and 1.99 g (10 mmol) of 4-bromo-phenacylbromide **1b**. Yield: 3.26 g (75%), yellow prisms (EtOH), mp 131°C; ir (KBr, cm^{-1}): 2938 (m), 2797 (m), 1586 (m), 1493 (m), 1447 (m), 1372 (m), 1290 (m), 1248 (m), 1229 (m), 1144 (m), 1071 (m), 1005 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 2.82 (s, 3H, Me), 3.43–3.45 (m, 8H, 4xN-CH$_2$), 3.90 (s, 2H, 6-CH$_2$), 7.69–7.91 (m, 4H, ArH), 10.63 (s, 1H, NH$^+$); ms (El, 70 eV): *m/z* (%) = 28 (51), 42 (46), 71 (100), 113 (19), 143 (9), 183 (9), 185 (2), 250 (4), 295 (8), 320 (4), 353(M$^+$, 8). *Anal*. Calcd. for $C_{14}H_{18}Br_2N_4S$ (434.19): C, 38.73 H, 4.18 N, 12.90. Found: C, 38.59 H, 4.17 N, 12.87. **Free base 4i**: Yield: 2.58 g (73%), yellow prisms (CHCl$_3$, precipitated with petroleum ether), mp 142°C. IR (KBr, cm^{-1}): 2938 (m), 2846 (m), 2796 (m), 1586 (m), 1493 (s), 1447 (m), 1408 (m), 1372 (m), 1351 (m), 1290 (m), 1249 (m), 1229 (m), 1144 (m), 1071 (m), 1004 (m); ^{1}H nmr (CDCl$_3$, 300 MHz): δ = 2.33 (s, 3H, Me), 2.47–2.50 (t, 4H, 2xN-CH$_2$), 3.52 (s, 2H, 6-CH$_2$, thiadiazine), 3.78–2.81 (t, 4H, 2xN-CH$_2$), 7.53–7.78 (m, 4H, ArH); ^{13}C nmr (CDCl$_3$, 50 MHz): δ = 22.21 (6-CH$_2$, thiadiazine), 46.01 (Me), 47.22 (CH$_2$), 54.60 (CH$_2$), 123.97 (Ar), 128.01 (ArH), 131.77 (ArH), 134.47 (Ar), 146.12 (5-C, thiadiazine), 151.56 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (34), 42 (37), 71 (100), 102 (20), 143 (10), 183 (3), 295 (9), 353 (M$^+$, 5). *Anal.* Calcd. for $C_{14}H_{17}BrN_4S$ (353.28): C, 47.60; H, 4.85; N, 1586. Found: C, 47.57; H, 4.82; N, 15.87.

2-(N-Methyl-piperazino)-5-(4-chlorophenyl)-6H-1,3,4-thiadiazine. **Hydrobromide 3j**: prepared from 1.74 g (10 mmol) of **2b** and 2.34 g (10 mmol) of 4-chloro-phenacylbromide **1c**. Yield: 2.73 g (70%), yellow prisms (EtOH), mp 184°C; ir (KBr, cm^{-1}): 2937 (m), 2799 (m), 1489 (s), 1446 (m), 1352 (m), 1291 (m), 1251 (m), 1145 (m), 1006 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 2.84 (s, 3H, Me), 3.40–3.47 (t, 4H, 2xN-CH$_2$), 3.80 (t, 4H, 2xN-CH$_2$), 4.41 (s, 2H, 6-CH$_2$, thiadiazine), 7.44–7.98 (m, 4H, ArH), 9.97 (s, 1H, NH$^+$); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 21.50 (6-CH$_2$, thiadiazine), 42.08 (Me), 43.99 (CH$_2$), 51.71 (CH$_2$), 128.38 (ArH), 128.61 (ArH), 134 (Ar), 134.43 (Ar), 147.25 (5-C, thiadiazine), 151.14 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (45), 71 (100), 83 (42), 113 (29), 143 (10), 206 (2), 216 (11), 251 (15), 276 (2), 308 (M$^+$, 14). *Anal*. Calcd. for $C_{14}H_{18}BrClN_4S$ (389.74): C, 43.14; H, 4.66; N, 14.38. Found: C, 43.09; H, 4.63; N, 14.37. **Free base 4j**: Yield: 2.16 g (70%), yellow prisms (EtOH), mp 142°C; ir (KBr, cm^{-1}): 2937 (m), 2797 (m), 1491 (s), 1447 (m), 1374 (m), 1352 (m), 1291 (m), 1250 (m), 1230 (m), 1145 (m), 1005 (m); ^{1}H nmr (CDCl$_3$, 300 MHz): δ = 2.29 (s, 3H, Me), 2.43–2.46 (t, 4H, 2xN-CH$_2$), 3.47 (s, 2H, 6-CH$_2$, thiadiazine), 3.73–3.77 (t, 4H, 2xN-CH$_2$), 7.33–7.79 (m, 4H, ArH); ms (El, 70 eV): *m/z* % = 42 (44), 71 (100), 83 (41), 110 (4), 143 (15), 238 (17), 251 (20), 276 (1), 308 (M$^+$, 13). *Anal*. Calcd. for $C_{14}H_{17}Cl$ N_4S (308.83): C, 54.45; H, 5.55; N, 18.14. Found: C, 54.50; H, 5.55; N, 18.13.

2-(N-Methyl-piperazino)-5-(4-fluorophenyl)-6H-1,3,4-thiadiazine. **Hydrobromide 3k**: prepared from 1.74 g (10 mmol) of **2b** and 2.17 g (10 mmol) of 4-fluoro-phenacylbromide **1d**. Yield:

2.95 g (79%), yellow prisms (EtOH), mp 175°C; ir (KBr, cm^{-1}): 2593 (m), 1499 (m), 1423 (m), 1241 (m); ^1H nmr (DMSO-d_6, 300 MHz): δ = 2.82 (s, 3H, Me), 3.33–3.45 (m, 8H, 4xN-CH_2), 3.79 (s, 2H, 6-CH_2, thiadiazine), 7.29–8.02 (m, 4H, ArH), 4.83 (s, 1H, NH_2); ^{13}C nmr (DMSO, 50 MHz): δ = 21.66 (6-CH_2, thiadiazine), 42.13 (Me), 44.07 (CH_2), 51.83 (CH_2), 115.30 (d, J(C,F) = 21.4, ArH), 128.86 (d, J(C,F) = 8.0, ArH), 131.74 (d, J(C,F) = 3.3, Ar), 150.95 (5-C, thiadiazine), 160,50 (d, J(C,F) = 247.4, Ar) 165.63 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (24), 57 (1), 80 (16), 95 (2), 122 (19), 146 (2), 162 (27), 189 (55), 216 (11), 247 (M^+, 100) 279 (4). *Anal*. Calcd. for $C_{14}H_{18}BrFN_4S$ (373.29): C, 45.05; H, 4.86; N, 15.01. Found: C, 45.10; H, 4.83; N, 14.98.

2-(N-Methyl-piperazino)-5-(4-methoxyphenyl)-6H-1,3,4-thiadiazine. **Hydrobromide 3l**: prepared from 1.74 g (10 mmol) of **2b** and 2.29 g (10 mmol) of 4-methoxy-phenacylbromide **1f**. Yield: 2.85 g (74%), yellow prisms (EtOH), mp 166°C; ir (KBr, cm^{-1}): 2928 (m), 2653 (m), 2602 (m), 2581 (m), 1604 (m), 1501 (s), 1467 (m), 1420 (m), 1379 (m), 1325 (m), 1253 (m), 1186 (m), 1022 (m), 975 (m); ^1H nmr (DMSO-d_6, 300 MHz): δ = 2.84 (s, 3H, Me), 3.39–3.43 (t, 4H, 2xN-CH_2), 3.77 (s, 2H, 6-CH_2, thiadiazine), 3.80–3.81 (t, 4H, 2xN-CH_2), 7.02–7.92 (m, 4H, ArH), 9.90 (s, 1H, NH^+); ^{13}C nmr (DMSO-d_6, 50 MHz) δ = 21.62 (6-CH_2, thiadiazine), 42.09 (Me), 44.10 (CH_2), 51.71 (CH_2), 55.22 (MeO), 113.99 (ArH), 127.38 (Ar), 128.23 (ArH), 147.80 (OAr), 150.79 (5-C, thiadiazine), 160.61 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (100), 71 (63), 91 (29), 119 (42), 135 (46), 202 (57), 234 (32), 247 (16), 275 (98), 304 (M^+, 19). *Anal*. Calcd. for $C_{15}H_{21}Br\ N_4OS$ (385.32): C, 46.76; H, 5.49; N, 14.54. Found: C, 46.69; H, 5.47; N, 19.52. **Free base 4k**: Yield: 2,22 g (73%), yellow prisms (EtOH), mp 117°C; ir (KBr, cm^{-1}): 1606 (m), 1498 (m), 1451 (m), 1291 (m), 1252 (m), 1223 (m), 1179 (m), 1027 (m); ^1H nmr ($CDCl_3$, 300 MHz): δ = 2.35 (s, 3H, Me), 2.49–2.52 (t, 4H, 2xN-CH_2), 3.53 (s, 2H, 6-CH_2, thiadiazine), 3.79 (s, 3H, Me), 3.85–3.87 (t, 4H, 2xN-CH_2), 6.94–7.87 (m, 4H, ArH); ms (El, 70 eV): *m/z* (%) = 28 (82), 71 (100), 83 (57), 133 (44), 135 (61), 185 (2), 213 (16), 234 (95), 247 (35), 272 (10), 304 (M^+, 97). *Anal*. Calcd. for $C_{15}H_{20}N_4OS$ (304.41): C, 59.18; H, 6.62; N, 18.40. Found: C, 58.99; H, 6.64; N, 18.35.

2-(N-Methyl-piperazino)-5-(4-nitrophenyl)-6H-1,3,4-thiadiazine. **Hydrobromide 3m**: prepared from 1.74 g (10 mmol) of **2b** and 2.44 g (10 mmol) of 4-nitro-phenacylbromide **1g**. Yield: 3.2 g (80%), yellow lamella (EtOH), mp 202°C; ir (KBr, cm^{-1}): 2923 (m), 1600 (m), 1519 (m), 1499 (m), 1346 (s), 1109 (m), 1090 (m), 1022 (m), 856 (m).; ^1H nmr (DMSO-d_6, 300 MHz): δ = 2.84 (s, 3H, Me), 3.44 (m, 8H, 4xN-CH_2), 3.94 (s, 2H, 6-CH_2), 8.19–8.35 (m, 4H, ArH); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 21.83 (6-CH_2, thiadiazine), 42.01 (Me), 44.47 (CH_2), 51.51 (CH_2), 123.79 (ArH), 127.91 (ArH), 140.64 (Ar), 147.76 (Ar), 148.02 (5-C, thiadiazine), 154.18 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (67), 71 (100), 82 (30), 124 (3), 143 (13), 171 (4), 196 (3), 217 (14), 262 (35), 287 (25), 319 (M^+, 26), 338 (6). *Anal*. Calcd. for $C_{14}H_{18}Br\ N_5O_2S$ (400.30): C, 42.01; H, 4.53; N, 17.50. Found: C, 42.02; H, 4.51; N, 17.53. **Free base 4l**: Yield: 2.46 g (77%), yellow lamella (EtOH), mp 149° C; ir (KBr, cm^{-1}): 1598 (m), 1514 (s), 1496 (s), 1445 (m), 1376 (m), 1345 (s), 1290 (m), 1250 (m), 1233 (m), 1144 (m), 859 (m); ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.35 (s, 3H,Me), 2.49–2.54 (t, 4H, 2xN-CH_2), 3.59 (s, 2H, 6-CH_2, thiadiazine) , 3.83–3.86 (t, 4H, 2xN-CH_2), 8.04–8.30 (m, 4H, ArH); ^{13}C nmr ($CDCl_3$, 50 MHz): δ = 22.07 (6-CH_2, thiadiazine), 45.97 (Me), 47.15 (CH_2), 54.57 (CH_2), 123.88 (ArH), 127.11 (ArH), 141.61 (Ar), 144.70 (Ar), 148.07 (5-C, Hetar), 151.67 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (62), 71 (100), 83 (26), 133 (3), 149 (4), 165 (1), 217 (2), 262 (13), 287 (3), 319 (M^+, 13). *Anal*. Calcd. for $C_{14}H_{17}N_5O_2S$ (319.38): C, 52.65; H, 5.37; N, 21.93. Found: C, 52.63; H, 3.36; N, 21.95.

2-(N-Methyl-piperazino)-5,6-diphenyl-6H-1,3,4-thiadiazine. **Free base 4m**: The title compound was prepared starting from 1.74 g (10 mmol) of **2b** and 2.75 g (10 mmol) of 2-bromo-1,2-diphenylethan-1-one **1h** as described for **4g**. Yield: 2.42 g (69%), orange prisms (EtOH), mp 176°C; ir (KBr, cm^{-1}): 3420 (m), 3212 (m), 2935 (m), 2798 (m), 1495 (s), 1469 (m), 1446 (m), 1293 (m), 1269 (m), 1157 (m), 1010 (m), 770 (m), 698 (s); ^1H nmr ($CDCl_3$, 300 MHz): δ = 2.32 (s, 3H, Me), 2.43–2.47 (t, 4H, 2xN-CH_2), 3.05–3.08 (t, 4H, 2xN-CH_2), 3.62 (s, 1H, 6-CH, thiadiazine); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 22.1 (6-CH_2, thiadiazine), 45.59 (Me), 48.97 (CH_2), 54.32 (CH_2), 126.19 (ArH), 127.51 (ArH), 127.76 (ArH), 128.23 (ArH), 128.30 (ArH), 128.45 (ArH), 129.24 (ArH), 137.70 (Ar), 148.18 (5-C, thiadiazine), 150.95 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (18), 43 (34), 77 (29), 105 (46), 143 (3), 178 (5), 192 (2), 234 (5), 248 (81), 303 (40), 318 (M^+, 100). *Anal*. Calcd. for $C_{20}H_{22}N_4S$ (350.48): C, 68.54; H, 6.33; N, 15.99. Found: C, 68.52; H, 6.19; N, 16.01. **Hydrochloride 3n**: Treatment of an ethanol solution of the free base **4m** with ethanolic hydrochloric acid yielded the hydrochlorides. Yield: 3.15 g (73%), orange prisms (EtOH), mp 285°C; ir (KBr, cm^{-1}): 3197 (m), 3023 (m), 2923 (m), 2845 (m), 2698 (m), 2654 (s), 2586 (s), 2517 (m), 2470 (m), 2445 (m), 1593 (m), 1497 (m), 1448 (m), 696 (m); ^1H nmr (DMSO-d_6, 300 MHz): δ = 2.77 (s, 3H, Me), 2.99–3.05 (t, 8H, 4xN-CH_2), 3.48 (s, 2H, 6-CH_2, thiadiazine), 7.24–7.35 (m, 10H, ArH); ms (El, 70 eV): *m/z* (%) = 28 (5), 43 (46), 72 (37), 116 (7), 151 (1), 178 (7), 191 (4), 217 (10), 248 (100), 303 (59), 318 (73), 350 (M^+, 2). *Anal*. Calcd. for $C_{20}H_{23}BrN_4S$ (431.39): C, 55.68, H, 5.37; N, 12.99. Found: C, 55.64; H, 5.36; N, 13.01.

2-Piperidino-5-(4-fluorphenyl)-6H-1,3,4-thiadiazine. **Hydrobromide 3o**: prepared from 1.59 g (10 mmol) of **1c** and 2.17 g (10 mmol) of 4-fluoro-phenacylbromide **1d**. Yield: 2.58 g (72%), yellow prisms (EtOH), mp 182°C; ir (KBr, cm^{-1}): 3038 (m), 2946 (m), 2897 (m), 2858 (m), 1595 (m), 1568 (s), 1513 (m), 1443 (m), 1361 (m), 1328 (m), 1228 (m), 854 (m); ^1H nmr (DMSO-d_6, 300 MHz): δ = 1.70 (m, 6H, 3xCH_2), 3.42–3.47 (t, 4H, 2xN-CH_2), 4.37 (s, 2H, 6-CH_2, thiadiazine), 7.39–8.03 (m, 4H, ArH), 13.07 (s, 1H, NH^+); ^{13}C NMR (DMSO-d_6, 50 MHz): δ = 22.79 (6-CH_2, thiadiazine), 23.90 (CH_2), 49.23 (CH_2), 115.77 (d, J(C,F) = 21.1, ArH), 124.00 (d, J(C,F) = 3.2, Ar), 128.51 (d, J (C,F) = 8.1, ArH), 153.32 (5-C, thiadiazine), 160.39 (d, J(C, F) = 247.3, Ar), 165.32 (2-C, thiadiazine); ms (El, 70 eV): *m/z* = 28 (80), 55 (21), 70 (89), 101 (22), 128 (100), 155 (7), 245 (11), 277 (M^+, 59). *Anal*. Calcd. for $C_{14}H_{17}BrFN_3S$ (358,27): C, 46.93; H, 4.78; N, 11.73. Found: C, 46.79; H, 4.77; N. 11.74.

2-Morpholino-5-(4-fluorophenyl)-6H-1,3,4-thiadiazine. **Hydrobromide 3p**: prepared from 1.61 g (10 mmol) of **2d** and 2.17 g (10 mmol) of 4-fluoro-phenacylbromide **1d**. Yield: 2.74 g (76%), yellow prisms (EtOH), mp 121°C; ir (KBr, cm^{-1}): 1601 (m), 1501 (m), 1448 (m), 1373 (m), 1350 (m), 1324 (m), 1269 (m), 1232 (m), 1114 (m), 887 (m); ^1H nmr (DMSO-d_6, 300 MHz): δ = 3.78–3.81 (t, 4H, 2xCH_2), 3.86–3.90 (t, 4H, 2xN-CH_2), 4.36 (s, 2H, 6-CH_2, thiadiazine), 7.39–8.01 (m, 4H, ArH); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 22.95 (6-CH_2, thiadiazine), 49.48 (CH_2), 64.94

(CH_2), 116.28 (d, J(C,F) = 21.2, ArH), 129.04 (d, J(C,F) = 3.2, Ar), 129.58 (d, J(C,F) = 8.1, ArH), 151.41 (5-C, thiadiazine), 161.80 (d, J(C,F) = 247.4, Ar), 166.42 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (29), 61 (13), 86 (89), 101 (20), 130 (100), 157 (2), 165 (3), 195 (4), 233 (3), 279 (M^+, 53). Anal. Calcd. for $C_{13}H_{15}BrFN_3OS$ (360.25): C, 43.34; H, 4.20; N, 11.66. Found: C, 43.21; H, 4.19; N, 11.66.

General procedure for the synthesis of 2-pyrrolidino-5-aryl-6-(4-nitrobenzylidene)-6H-1,3,4-thiadiazines 5a,b. The free base of the thiadiazines **4a,b** (10 mmol) and 1.5 g (10 mmol) of 4-nitrobenzaldehyde in 20 mL of ethanol was refluxed for 10 min. The precipitated product was separated by filtration. The residue was extracted with boiling ethanol and recrystallized from pyridine.

2-Pyrrolidino-5-phenyl-6-(4-nitrobenzylidene)-6H-1,3,4-thiadiazine (5a). From 2.45 g (10 mmol) of **4a** and 1.5 g (10 mmol) of 4-nitrobenzaldehyde. Yield: 3.32 g (73%), yellow prisms (EtOH), mp 186°C; ir (KBr, cm^{-1}): 3420 (m), 3168 (m), 3072 (m), 2869 (m), 1515 (s), 1481 (m), 1458 (m), 1396 (m), 1344 (s), 853 (m), 695 (m); ^1H nmr (DMSO-d_6, 300 MHz): δ = 1.88–1.90 (m, 4H, 2xCH_2), 3.41–3.46 (t, 4H, 2xN-CH_2), 7.43–8.20 (m, 9H, ArH), 9.7 (s, 1H, CH); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 24.27 (CH_2), 40.01 (6-C, thiadiazine), 47.29 (CH_2), 70.11 (CH), 122.61 (ArH), 126.59 (ArH), 128.14 (ArH), 128.24 (ArH), 128.62 (ArH), 137.0 (Ar), 143.74 (Ar), 144.26 (Ar), 146.94 (5-C, thiadiazine), 149.06 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 28 (100), 55 (35), 77 (39), 113 (76), 150 (46), 176 (67), 199 (14), 245 (38), 296 (20), 378 (M^+, 8). *Anal*. Calcd. for $C_{26}H_{22}N_4O_2S$ (454.54): C, 68.70; H, 4.88; N, 12.33. Found: C, 68.74; H, 4.8;9 N, 12.31.

2-Pyrrolidino-5-(4-bromophenyl)-6-(4-nitrobenzylidene)-6H-1,3,4-thiadiazine (5b). Prepared from 3.24 g (10 mmol) of **4b** and 1.5 g (10 mmol) of 4-nitrobenzaldehyde. Yield: 3.24 g (71%), orange prisms (EtOH), mp 174°C; ir (KBr, cm^{-1}): 3421 (m), 1517 (s), 1481 (m), 1456 (m), 1369 (m), 1345 (m), 1322 (m), 1073 (m), 835 (m); ^1H NMR (DMSO-d_6, 300 MHz): δ = 1.88–1.90 (m, 4H, 2xCH_2), 4.67–4.69 (t, 4H, 2xN-CH_2), 7.47–8.23 (m, 8H, ArH), 9.7 (s, 1H, CH); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 25.4 (CH_2), 46.64 (6-C, thiadiazine); 47.65 (CH_2), 122.31 (CH), 122.73 (ArH), 128.34 (ArH), 128.65 (ArH), 131.15 (ArH), 136.13 (Ar), 143.92 (Ar), 147.03 (Ar), 148.94 (5-C, thiadiazine), 154.36 (2-C, thiadiazine); ms (El, 70 eV): *m/z* (%) = 323 (2), 345 (9), 347 (3), 442 (2), 444 (1), 458 (M^+, 1). *Anal*. Calcd. for $C_{20}H_{17}BrN_4O_2S$ (457.34): C, 52.52; H, 3.75; N, 12.25. Found: C, 52.49; H, 3.72; N, 12.22.

General procedure for the synthesis of 1-acetyl-3-pyrrolidino-4-acetylmercapto-5-aryl-pyrazoles (6a–c) and 1-Acetyl-3-(N-methyl-piperazino)-4-acetylmercapto-5-(4-bromophenyl)-pyrazole (6d). The free base of the 1,3,4-thiadiazine (10 mmol) in 6 mL acetic acid was refluxed for 1 h. The mixture was concentrated *in vacuo* to afford oil. The product was washed with water and recrystallized from ethanol.

1-Acetyl-3-pyrrolidino-4-acetylmercapto-5-phenyl-pyrazole (6a). Prepared from 2.45 g (10 mmol) of **4a**. Yield: 2.11 g (64%), colourless prisms (EtOH), mp 99°C; ir (KBr, cm^{-1}): 1732 (s), 1701 (s), 1562 (s), 1528 (m), 1423 (s), 1464 (s), 1346 (m), 1315 (s), 1284 (s), 1133 (m), 1109 (m), 932 (m), 621 (m); ^1H nmr ($CDCl_3$; 300 MHz): δ = 1.90–1.94 (m, 4H, 2xCH_2), 2.25 (s, 3H, Me), 2.59 (s, 3H, Me), 3.50–3.55 (t, 4H, 2xN-CH_2), 7.19–7.39 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 23.28 (Me), 25.37 (CH_2), 29.40 (Me), 99.42 (4-C, Hetar), 127.71 (ArH), 128.81 (ArH), 128.95 (ArH), 130.37 (Ar), 150.56 (5-C, Hetar), 156.95 (3-C, Hetar), 169.22 (C=O), 194.93 (C=O); ms (El, 70 eV): *m/z* (%) = 28 (31), 71 (9), 104 (6), 121 (1), 148 (3), 204 (11), 216 (2), 245 (100), 287 (32), 329 (M^+, 43). *Anal*. Calcd. for $C_{17}H_{19}N_3O_2S$ (329.42): C, 61.98; H, 5.81; N, 12.76. Found: C, 61,79; H, 5,83; N, 12.73.

1-Acetyl-3-pyrrolidino-4-acetylmercapto-5-(4-bromophenyl)-pyrazole (6b). From 3.24 g (10 mmol) of **4b**. Yield: 2.82 g (69%), colourless prisms (EtOH), mp 134°C; ir (KBr, cm^{-1}): 1729 (s), 1705 (s), 1564 (s), 1530 (s), 1421 (s), 1365 (s), 1347 (m), 1316 (s), 1282 (s), 1107 (m), 932 (m), 617 (m); ^1H nmr ($CDCl_3$, 300 MHz): δ = 1.90–1.94 (m, 4H, 2xCH_2), 2.27 (s, 3H, Me), 2.59 (s, 3H, Me), 3.49–3.53 (t, 4H, 2xN-CH_2), 7.13–7.35 (m, 4H, ArH); ms (El, 70 eV): *m/z* (%) = 28 (7), 43 (40), 71 (17), 138 (7), 140 (3), 183 (5), 238 (16), 244 (16), 279 (100), 321 (37), 363 (43), 408 (M^+, 3). *Anal*. Calcd. for $C_{17}H_{18}BrN_3O_2S$ (408.31): C, 50.01; H, 4.44; N, 10.29. Found: C, 50.01; H, 4.43; N, 10.28.

1-Acetyl-3-pyrrolidino-4-acetylmercapto-5-(4-chlorophenyl)-pyrazole (6c). From 2.8 g (10 mmol) of **4c**. Yield: 2.44 g (67%), colourless prisms (EtOH), mp 131°C; ir (KBr, cm^{-1}): 1730 (s), 1703 (s), 1561 (s), 1531 (m), 1422 (s), 1365 (s), 1344 (m), 1317 (s), 1301 (m), 1282 (m), 1105 (m), 1091 (m), 934 (m), 840 (m), 618 (m); ^1H nmr ($CDCl_3$, 300 MHz): δ = 1.90–1.94 (m, 4H, 2xCH_2), 2.27 (s, 3H, Me), 2.59 (s, 3H, Me), 3.50–3.52 (t, 4H, 2xN-CH_2), 7.13–7.35 (m, 4H, ArH); ^{13}C nmr ($CDCl_3$, 50 MHz): δ = 23.23 (Me), 25.36 (CH_2), 29.44 (Me), 48.42 (CH_2), 99.62 (4-C, Hetar), 128.05 (ArH), 128.79 (Ar), 130.41 (ArH), 134.91 (Ar), 149.33 (5-C, Hetar), 156.91 (3-C, Hetar), 169.33 (C=O), 194.57 (C=O); ms (El, 70 eV): *m/z* (%) = 28 (39), 43 (40), 71 (13), 113 (1), 138 (5), 183 (3), 204 (1), 238 (12), 247 (3), 279 (100), 321 (34), 363/365 (M^+, 40/13). *Anal*. Calcd. for $C_{17}H_{18}ClN_3O_2S$ (363.86): C, 56.12; H, 4.99; N, 11.55. Found: C, 56.14; H, 4.97; N, 11.54.

1-Acetyl-3-(N-methyl-piperazino)-4-acetylmercapto-5-(4-bromophenyl)-pyrazole (6d). From 3.53 g (10 mmol) of **4i**. Yield: 3.10 g (71%), colourless prisms (washed with H_2O), mp 154°C; ir (KBr, cm^{-1}): 2938 (m), 2841 (m), 2798 (m), 1561 (m), 1504 (m), 1451 (m), 1369 (m), 1324 (m), 1283 (m), 1008 (m), 828 (m); ^1H nmr (DMSO-d_6, 300 MHz): δ = 0.89 (s, 3H, Me), 1.05 (s, 3H, Me), 2.31 (s, 3H, N-CH_3), 3.22–3.36 (m, 8H, 4xN-CH_2), 7.43–7.63 (m, 4H, ArH); ^{13}C nmr ($CDCl_3$, 50 MHz): δ = 46.10 (Me), 48.23 (CH_2), 54.53 (CH_2), 129.41 (ArH), 131.06 (ArH), 131.40 (ArH); ms (El, 70 eV): *m/z* (%) = 28 (84), 43 (100), 83 (17), 129 (7), 182 (7), 252 (21), 282 (17), 320 (16), 352 (13), 394 (22), 439 (M^+, 2). *Anal*. Calcd. for $C_{18}H_{21}Br\ N_4O_2S$ (437.36): C, 49.43; H, 4.84; N, 12.81. Found: C, 49.41; H, 4.82; N, 12.83.

General procedure for the synthesis of 3-pyrrolidino-, 3-piperidino, and 3-morpholino-5-aryl-pyrazoles 7a–i and 9a–c. The free base of the 1,3,4-thiadiazine (10 mmol) in 15 mL of glacial acetic acid was refluxed for 2 h. The hot solution was filtered. The precipitated product was recrystallized from ethanol. Treatment of an ethanol solution of the free base of **7a–i** with ethanolic hydrochloric acid or hydrobromic acid (48%) yielded the hydrochlorides and hydrobromides, respectively. In case of **9a–c**, the solvent was evaporated *in vacuo*. Standing of the oil in the refrigerator for several days resulted in crystallization. The pyrazoles **9a–c** were recrystallized from ethanol.

3-Pyrrolidino-5-phenyl-pyrazole (7a). *Free base*: From 2.45 g (10 mmol) of **4a** in glacial acetic acid. Yield: 1.55 g (73%), colourless prisms ($CHCl_3$/petroleum ether), mp 183°C. *Hydrochloride*: 3.29 g (10 mmol) of **6a** was refluxed in conc. aq. HCl for 1 h. Yield: 1.49 g (71%); ir (KBr, cm^{-1}): 3430 (m), 3250 (m), 2967 (m), 2873 (m), 2849 (m), 1603 (m), 1572 (m), 1542

(m), 1482 (m), 1461 (m), 736 (m), 695 (m), 539 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.95–1.99 (m, 4H, 2xCH_2), 3.30–3.35 (t, 4H, 2xN-CH_2), 5.77 (s, 1H, NH), 7.31–7.92 (m, 6H, ArH, Hetar), 7.31–7.92 (m, 5H, ArH), 5.77 (s, 1H, NH), 7.31–7.92 (m, 5H, ArH); ^{13}C nmr ($CDCl_3$, 50 MHz): δ = 25.23 (CH_2), 48.29 (CH_2), 86.14 (4-C, Hetar), 125.33 (ArH), 127.50 (ArH), 128.49 (ArH), 131.24 (Ar), 145.78 (5-C, Hetar), 156.27 (3-C, Hetar); ms (El, 70 eV): *m/z* (%) = 28 (13), 41 (4), 71 (12), 77 (8), 104 (6), 115 (4), 144 (9), 158 (8), 185 (35), 213 (M^+, 100). *Anal*. Calcd. for $C_{13}H_{15}N_3$ (213.28): C, 73.21; H, 7.09; N, 19.70. Found: C, 73.23; H, 7.07; N, 19.68.

3-Pyrrolidino-5-(4-bromophenyl)-pyrazole (7b). *Free base*: From 3.24 g (10 mmol) of **4b** in glacial acetic acid. Yield: 2.07 g (71%), colourless prisms (EtOH), mp 217°C. *Hydrochloride*: 4.08 g (10 mmol) of **6b** was refluxed in con. HCl for 1 h. Yield 2.16 g (74%); ir (KBr, cm^{-1}): 3163 (m), 3136 (m), 3063 (m), 3000 (m), 2966 (m), 2931 (m), 2896 (m), 2848 (m), 1606 (m), 1547 (s), 1486 (m), 1467 (m), 827 (m), 742 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.93–1.98 (m, 4H, 2xCH_2), 3.24–3.26 (t, 4H, 2xN-CH_2), 5.64 (s, 1H, NH), 7.47–7.49 (m, 5H, ArH, H-Hetar); ^{13}C NMR (DMSO–d_6, 50 MHz): δ = 24.43 (CH_2), 48.29 (CH_2), 84.2 (4-C, Hetar), 119.86 (Ar), 126.55 (ArH), 131.14 (ArH), 145.78 (5-C, Hetar), 156.3 (3-C, Hetar), ms (El, 70 eV): *m/z* (%) = 28 (91), 71 (6), 263 (10), 291/293 (M^+, 100/85). *Anal*. Calcd. for $C_{13}H_{14}Br\ N_3$ (292,17): C, 53.44; H, 4.83; N, 14.38. Found: C, 53.42; H, 4.82; N, 14.39.

3-Pyrrolodino-5-(4-chlorophenyl)-pyrazole (7c). *Free base*: From 2.80 g (10 mmol) of **4c** in glacial acetic acid. Yield: 1.88 g (76%), colourless prisms (EtOH), mp 215°C. *Hydrochloride*: 3.63 g (10 mmol) of **6c** was refluxed in conc. HCl for 1 h. Yield: 1.80 g (73%); ir (KBr, cm^{-1}): 3166 (m), 3143 (m), 3085 (m), 3064 (m), 3007 (m), 2958 (m), 2844 (m), 1607 (m), 1546 (s), 1489 (m), 1459 (m), 1092 (m), 831 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.96–2.01 (m, 4H, 2xCH_2), 3.28–3.33 (t, 4H, 2xN-CH_2), 5.69 (s, 1H, NH), 7.31–7.58 (m, 5H, ArH, H-Hetar); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 24.66 (CH_2), 48.65 (CH_2), 86.1 (4-C, Hetar), 126.38 (ArH), 138.48 (ArH), 131.58 (Ar), 145.7 (5-C, Hetar), 156.3 (3-C, Hetar); ms (El, 70 eV): *m/z* (%) = 28 (34), 91 (4), 248 (M^+, 19). *Anal*. Calcd. for $C_{13}H_{14}ClN_3$ (247.72): C, 63.03; H, 5.70; N, 16.96. Found: C, 62.99; H, 5.68; N, 16.97.

3-Pyrrolidino-5-(4-fluorophenyl)-pyrazole (7d). *Hydrochloride*: From 2.63 g (10 mmol) of **4d** in glacial acetic acid. Treatment of an ethanol solution of the free base with ethanolic hydrochloric acid yielded the hydrochlorides. Yield: 1.82 g (68%), colourless prisms (EtOH), mp 169°C, ir (KBr, cm^{-1}): 3423 (m), 3106 (m), 2976 (m), 2932 (m), 2877 (m), 2770 (m), 1636 (s), 1596 (m), 1574 (m), 1503 (m), 1460 (m), 1234 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 1.94–1.98 (m, 4H, 2xCH_2), 3.35–3.39 (t, 4H, 2xN-CH_2), 6.36 (s, 1H, NH), 7.35–8.02 (m, 5H, ArH, H-Hetar); ms (El, 70 eV): *m/z* (%) = 28 (23), 55 (3), 71 (5), 113 (5), 120 (5), 146 (1), 162 (6), 203 (21), 230 (43), 231 (M^+, 100). *Anal*. Calcd. for $C_{13}H_{15}ClFN_3$ (267.73): C, 58.32; H, 5.65; N, 15.70. Found: C, 58.35; H, 5.63; N, 15.72.

3-Pyrrolidino-5-(4-methoxyphenyl)-pyrazole (7e). *Free base*: From 3.12 g (10 mmol) of **3f** in glacial acetic acid. To an EtOH solution of the reaction product was added a dilute aqueous solution of ammonia until pH = 8 was reached. Yield: 1.93 g (69%), colourless prisms (EtOH), mp 183°C; ir (KBr, cm^{-1}): 2977 (m), 2837 (m), 2744 (m), 1632 (m), 1605 (m), 1580 (s), 1463 (m), 1316 (m), 1256 (m), 1182 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 1.96–2.01 (m, 4H, 2xCH_2), 3.60–3.74 (t, 4H, 2xN-CH_2), 4.29 (s, 3H, MeO), 7.05–7.92 (m, 5H, ArH, Hetar); ms (El, 70 eV): *m/z* (%) = 28 (38), 55 (7), 73 (6), 113 (20), 133 (10), 146 (1), 174 (7), 188 (5), 215 (26), 243 (M^+, 100). *Anal*. Calcd. for $C_{14}H_{18}ClN_3O$ (279.77): C, 60.10; H, 6.49; N, 15.02. Found: C, 59.98; H, 6.42; N, 15.02.

3-Pyrrolidino-5-(4-nitrophenyl)-pyrazole (7f). *Free base*: From 2.90 g (10 mmol) of **4f** in glacial acetic acid. Yield: 1.88 g (73%), colourless rods (EtOH), mp 154°C; ir (KBr, cm^{-1}): 2954 (m), 2869 (m), 2361 (m), 1600 (m), 1577 (m), 1551 (m), 1517 (s), 1496 (s), 1456 (m), 1338 (s), 855 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.97–2.05 (t, 4H, 2xCH_2), 3.30–3.35 (t, 4H, 2xN-CH_2), 5.75 (s, 1H, NH), 7.82–8.29 (m, 5H, ArH, Hetar); ms (El, 70 eV): *m/z* (%) = 28 (63), 65 (47), 71 (19), 96 (7), 128 (21), 160 (14), 183 (3), 192 (6), 230 (12), 258 (M^+, 100). *Anal*. Calcd. for $C_{13}H_{14}N_4O_2$ (258.28): C, 60.45; H, 5.46; N, 21.69. Found: C, 60.45; H, 5.45; N, 21.67.

3-Pyrrolidino-4.5-diphenyl-pyrazole (7g). *Hydrobromide*: From 3.21 g (10 mmol) **4g** as described by general procedure in glacial acetic acid. Treatment of an ethanol solution of the free base with hydrobromic acid (48%) yielded the hydrobromides. Yield: 2.63 g (71%), colourless prisms (EtOH), mp 202°C; ir (KBr, cm^{-1}): 3425 (m), 3219 (m), 3064 (m), 2964 (m), 1507 (s), 1480 (m), 1443 (m), 775 (m), 700 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.79–1.83 (m, 4H, 2xCH_2), 3.09–3.14 (t, 4H, 2xN-CH_2), 7.21–7.31 (m, 10H, 2xArH); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 24.28 (CH_2), 49.28 (CH_2), 104.1 (4-C, Hetar), 126.22 (ArH), 127.05 (ArH), 127.29 (ArH), 127.83 (ArH), 128.10 (ArH), 130 (ArH), 134.52 (Ar), 145.7 (5-C, Hetar), 156.41 (3-C, Hetar); ms (El, 70 eV): *m/z* (%) = 51 (11), 77 (20), 95 (1), 128 (1), 151 (8), 183 (12), 201 (15), 260 (1), 277 (100), 289 (M^+/7). *Anal*. Calcd. for $C_{19}H_{20}Br\ N_3$ (370,29): C, 61.63; H, 5.44; N, 11.35. Found: C, 61.62; H, 5.44 N, 11.38. *Free base*: (a) To an EtOH solution of 3.70 g (10 mmol) of hydrobromide **7g** was added a dilute aqueous solution of ammonia until pH = 8 was reached. Yield: 2.05 g (71%), colourless prisms, mp 211°C; (b) 3.21 g (10 mmol) of 2 h in an ethanol solution of sodium ethanolate (prepared from 0.23 g, 10 mmol, of sodium and 10 mL of ethanol) was refluxed for 1 h. Yield: 2.17 g (75 %); ir (KBr, cm^{-1}): 3217 (m), 3098 (m), 3065 (m), 2965 (m), 2860 (m), 1581 (m), 1505 (s), 1480 (m), 1443 (m), 1353 (m), 1294 (m), 1151 (m), 775 (m), 739 (m), 701 (s), 621 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.78–1.83 (m, 4H, 2xCH_2), 3.09–3.12 (t, 4H, 2xN-CH_2) 5.00 (s, 1H, NH), 7.24–7.31 (m, 10H, 2xArH); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 24.28 (CH_2), 49.25 (CH_2), 104.84 (4-C), 126.23 (ArH), 127.04 (ArH), 127.29 (ArH), 127.84 (ArH), 128.11 (ArH), 130.82 (ArH), 131.26 (Ar), 134.52 (Ar), 145.7 (5-C, Hetar), 156.41 (3-C, Hetar); ms (El, 70 eV): *m/z* (%) = 28 (54), 65 (40), 91 (10), 128 (12), 160 (14), 178 (3), 192 (5), 220 (4), 260 (19), 289 (M^+, 100), 297 (5). *Anal*. Calcd. for $C_{19}H_{19}N_3$ (289.37): C, 78.86; H, 6.62; N, 14.52. Found: C, 78.79; H, 6.63; N, 14.53.

3-Piperidino-5-(4-fluorophenyl)-pyrazole hydrochloride (7h). From 3.58 g (10 mmol) of **3o** in glacial acetic acid. Yield: 2.06 g (73%), colourless prisms (EtOH), mp 172°C; ir (KBr, cm^{-1}): 3053 (m), 2937 (m), 2854 (s), 2743 (s), 2691 (m), 1614 (s), 1564 (m), 1502 (m), 1454 (m), 1234 (m), 1170 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.65–1.73 (m, 6H, 3xCH_2), 3.46–3.50 (t, 4H, 2xN-CH_2), 5.58 (s, 1H, NH), 7.13–7.96 (m, 5H, ArH, Hetar); ms (El, 70 eV): *m/z* (%) = 36 (23), 68 (7), 84 (4), 128 (s), 162 (4), 190 (5), 216 (25), 245 (M^+, 100). *Anal*. Calcd. for $C_{14}H_{17}ClFN_3$ (281.76): C, 59.68; H, 6.08; N, 14.91. Found: C, 59.66; H, 6.09; N, 14.93.

3-Morpholino-5-(4-fluorophenyl)-pyrazole hydrochloride (7i). The title compound was prepared starting from 3.60 g (10 mmol) of **3p** in glacial acetic acid. Yield: 2.33 g (71%), colourless prisms (EtOH), mp 264°C; ir (KBr, cm^{-1}): 3022 (m), 2964 (m), 2891 (m), 2858 (m), 2756 (m), 1618 (s), 1563 (m), 1501 (m), 1467 (m), 1449 (m), 1236 (m), 1119 (m), 904 (m), 772 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 3.11–3.14 (t, 4H, 2xN-CH_2), 3.70–3.75 (t, 4H, 2xO-CH_2), 4.21 (s, br, 1H, NH^+), 7.32–7.87 (m, 5H, ArH, Hetar); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 47.53 (CH_2), 65.17 (CH_2), 88.53 (4-C, Hetar), 115.78 (ArH), 129.44 (ArH), 140.43 (Ar), 155.43 (5-C, Hetar), 160.22 (Ar), 165.17 (3-C, Hetar); ms (El, 70 eV): *m/z* (%) = 28 (24), 57 (1), 80 (16), 95 (7), 122 (19), 146 (2), 162 (27), 189 (55), 216 (11), 247 (M^+, 100), 279 (4). *Anal*. Calcd. for $C_{13}H_{15}BrFN_3O$ (328.18): C, 47.58; H, 4.61; N, 12.80. Found: C, 47.51; H, 4.58; N, 12.79.

General procedure for the synthesis of 3,3-bis(pyrrolidino)-5,5-diaryl-pyrazolyl-(4,4′)-disulfide (8a–c). The respective diacetyl-pyrazole (10 mmol) **6a–c** was refluxed in 20 mL of a 2*M* aq. solution of sodium hydroxide for 15 min. The product was filtered, washed thoroughly with water, and recrystallized from ethanol.

3,3-Bis(pyrrolidino)-5,5-diphenyl-pyrazolyl-(4,4′)-disulfide (8a). From 3.29 g (10 mmol) of **6a**. Yield: 1.71 g (70%), yellow prisms (EtOH), mp 115°C; ir (KBr, cm^{-1}): 1732 (s), 1702 (s), 1562 (s), 1528 (m), 1423 (m), 1365 (s), 1346 (m), 1315 (s), 1284 (m), 1133 (m), 1109 (m), 932 (m), 620 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.85–1.90 (m, 8H, 4xCH_2), 3.40 (t, 8H, 4xN-CH_2), 7.16–7.58 (m, 10H, 2xArH); ^{13}C nmr ($CDCl_3$, 50 MHz): δ = 25.36 (CH_2), 48.40 (CH_2), 99.41 (4-C, Hetar), 127.71 (ArH), 128.94 (ArH), 130.36 (Ar), 150.56 (5-C, Hetar), 156.95 (2-C, Hetar); ms (El, 70 eV): *m/z* (%) = 28 (29), 71 (12), 104 (13), 148 (8), 185 (2), 202 (17), 244 (100), 275 (1), 488 (M^+, 1). *Anal*. Calcd. for $C_{26}H_{28}N_6S_2$ (488,68): C, 127.8; H, 11.56; N, 34.40. Found: C, 126.9; H, 11.51; N, 34.12.

3,3-Bis(pyrrolidino)-5,5-bromophenyl-pyrazolyl-(4,4′)-disulfide (8b). From 4.08 g (10 mmol) of **6b**. Yield: 2.10 g (65%), yellow prisms (EtOH), mp 227°C; ir (KBr, cm^{-1}): 3207 (m), 2970 (m), 2869 (m), 1588 (m), 1570 (m), 1542 (m), 1486 (m), 1460 (m), 1438 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 1.81 (t, 4H, 2xCH_2), 5.7 (s, br, 2H, 2xNH), 7.40–7.73 (m, 8H, ArH). *Anal*. Calcd. for $C_{26}H_{26}Br_2N_6S_2$ (646.46): C, 96.62; H, 8.10; N, 26.00. Found: C, 96.65; H, 8.03; N, 26.31.

3,3-Bis(pyrrolidino)-5,5-chlorophenyl-pyrazolyl-(4,4′)-disulfide (8c). From 3.64 g (10 mmol) of **6c**. Yield: 1.79 g (64%), yellow prisms (EtOH), mp 229°C; ir (KBr, cm^{-1}): 3204 (m), 2970 (m), 1588 (m), 1541 (m), 1484 (m), 1460 (m), 1438 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.89–2.03 (t, 4H, 2xCH_2), 3.69–3.76 (m, 4H, 2xCH_2), 7.40–7.60 (m, 10H, ArH); ms (El, 70 eV): *m/z* (%) = 28 (61), 77 (100), 93 (26), 146 (31), 189 (46), 248 (100), 279 (47), 336 (13), 395 (11), 557 (M^+, 1). *Anal*. Calcd. for $C_{26}H_{26}Cl_2N_6S_2$ (557.56): C, 112.02; H, 9.40; N, 30.14. Found: C, 112.13; H, 9.35; N, 30.08.

3-(N-Methyl-piperazino)-5-(4-bromophenyl)-pyrazole (9a). *Hydrochloride*: From 3.53 g (10 mmol) of **4i** in glacial acetic acid. Yield: 2.57 g (72%). **6d** was refluxed in conc. aq. HCl for 1 h. Yield from **6d**: 2.61 g (73%), colourless prisms (EtOH), mp 178° C; ir (KBr, cm^{-1}): 3415 (s), 3142 (m), 2915 (m), 2852 (m), 2686 (s), 2604 (m), 2476 (m), 1619 (s), 1557 (m), 1455 (m), 1401 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 2.98 (s, 3H, N-Me), 3.14–3.18 (t, 4H, 2xN-CH_2), 3.83–3.91 (t, 4H, 2xN-CH_2), 5.28 (s, 1H, NH), 7.41–7.74 (m, 5H, ArH, Hetar); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 41.96 (Me), 44.72 (CH_2), 51.14 (CH_2), 89.32 (4-C, Hetar), 127.53 (ArH), 127.93 (Ar), 131.99 (ArH), 149.11 (Ar), 146.43 (5-C, Hetar), 157.57 (3-C, Hetar); ms (El, 70 eV): *m/z* (%) = 72 (17), 83 (3), 114 (3), 143 (1), 182 (3), 195 (1), 224 (1), 250 (15), 320 (12), 321 (M^+, 2). *Anal*. Calcd. for $C_{14}H_{18}BrClN_4$ (357.68): C, 47.01; H, 5.07; N, 15.66. Found: C, 46.96; H, 5.02; N, 15.63.

3-(N-Methyl-piperazino)-5-(4-chlorphenyl)-pyrazol (9b). *Hydrochloride*: From 3.08 g (10 mmol) of **4j** in glacial acetic acid. Yield: 2.25 g (72%), colourless prisms (EtOH), mp 181°C; ir (KBr, cm^{-1}): 3426 (m), 3135 (m), 3015 (m), 2962 (m), 2924 (m), 2674 (m), 1630 (m), 1451 (m), 1402 (s); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 2.98 (s, 3H, Me), 3.14–3.23 (t, 4H, 2xN-CH_2), 3.82–3.87 (t, 4H, 2xN-CH_2), 7.36–7.77 (m, 5H, ArH, H-Hetar), 11.3 (s, 1H, NH); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 41.98 (Me), 44.77 (CH_2), 51.21 (CH_2), 89.28 (4-C, Hetar), 127.16 (ArH), 127.48 (Ar), 127.95 (Ar), 128.92 (ArH), 146.31 (5-C, Hetar), 157.55 (3-C, Hetar); ms (El, 70 eV): *m/z* (%) = 28 (48), 51 (12), 77 (19), 107 (8), 151 (10), 183 (38), 201 (14), 213 (4), 262 (42), 277 (M^+, 100). *Anal*. Calcd. for $C_{14}H_{18}Cl_2N_4$ (313,23): C, 53.68; H, 5.79; N, 17.89. Found: C, 53.67; H, 5.81; N, 17.88.

3-(N-Methyl-piperazino)-4.5-diphenyl-pyrazole (9c). *Free base*: (a) From 3.5 g (10 mmol) of free base **4m**. Reaction time: 45 min. Yield: 2.16 g (68%), colourless needles (EtOH), mp 199°C; (b) 3.5 g (10 mmol) of **3g** and an ethanol solution of sodium ethanolate (prepared from 0.23 g, 10 mmol, of sodium and 10 mL of ethanol) was refluxed for 1 h. Yield: 2.42 g (76%); ir (KBr, cm^{-1}): 3421 (s), 3232 (m), 3066 (m), 2935 (m), 2838 (m), 2805 (m), 1494 (m), 1472 (m), 1447 (m), 1010 (m), 771 (m), 698 (s); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 2.29 (s, 3H, N-Me), 2.42–2.45 (t, 4H, 2xN-CH_2), 3.04–3.07 (t, 4H, 2xN-CH_2), 7.25–7.39 (m, 10H, 2xArH); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 45.68 (Me), 49.05 (CH_2), 54.39 (CH_2), 107.2 (4-C, Hetar), 126.16 (ArH), 127.50 (ArH), 127.71 (ArH), 128.20 (ArH), 128.26 (ArH), 129.27 (ArH), 133.75 (Ar), 145.7 (5-C, Hetar), 156.42 (3-C, Hetar); ms (El, 70 eV): *m/z* (%) = 43 (28), 72 (33), 84 (5), 116 (3), 159 (2), 178 (3), 191 (2), 234 (7), 248 (100), 274 (2), 318 (M^+, 88). *Anal*. Calcd. for $C_{20}H_{22}N_4$ (318.42): C, 75.44; H, 6.96; N, 17.60. Found: C, 75.45; H, 7.01; N, 17.60.

General procedure for the synthesis of 3-pyrrolidino-, 3-piperidino-, and 3-morpholino-4-ethoxycarbonyl-5-methyl-pyrazole hydrochlorides 10a–c and 3-morpholino-4-acetyl-5-methyl-pyrazole hydrochloride 10d. 4,4-Disubstituted thiosemicarbazides **2a,c,d** (10 mmol) and 1.65 g (10 mmol) of ethyl α-chloro-acetoacetate **1i** or 1.3 g (10 mmol) of α-chloro-acetylacetone **1j** in 10 mL of ethanol were refluxed for 1 h (**10d**: 5 min). After cooling and rapid filtration, the product was recrystallized from ethanol.

3-Pyrrolidino-4-ethoxycarbonyl-5-methyl-pyrazole (10a). *Hydrochloride*: From 1.45 g (10 mmol) of **2a**. Yield: 1.98 g (76%), colourless prisms (EtOH), mp 122°C; ir (KBr, cm^{-1}): 2988 (m), 2937 (s), 2860 (s), 2798 (s), 2757 (s), 2708 (s), 2680 (s), 1712 (s), 1600 (s), 1518 (m), 1457 (s), 1326 (s), 1132 (s), 1112 (m); ^{1}H nmr (DMSO-d_6, 300 MHz): δ = 1.25–1.30 (t, 3H, Me), 1.89–1.94 (m, 4H, 2xCH_2), 2.39 (s, 3H, Me), 3.42–3.47 (t, 4H, 2xN-CH_2), 4.17–4.24 (t, 2H, CH_2-O), 11.47 (s, 1H, NH^+); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 12.10 (Me), 14.02 (Me), 24.64 (CH_2), 51.48 (CH_2), 59.87 (CH_2), 97.42 (4-C, Hetar), 147.97 (5-C, Hetar), 150.38 (3-C, Hetar), 161.68 (C=O); ms (El, 70 eV): *m/z* (%) = 36 (78), 76 (5), 91 (28), 107 (9), 136 (5), 148 (49), 176 (82), 194 (69), 223 (M^+, 100). *Anal*. Calcd. for $C_{11}H_{18}ClN_3O_2$ (259,73): C, 50.87; H, 6.99; N, 16.18. Found: C, 50.83; H, 6.98; N, 16.21.

3-Piperidino-4-ethoxycarbonyl-5-methyl-pyrazole (10b). *Hydrochloride*: From 1.59 g (10 mmol) of **2c**. To the mixture was added, after 10 min, 1 mL of ethanolic hydrochloric acid. The hydrochloride precipitated when the solution was added dropwise to 100 mL of ether. Yield: 2.11 g (77%), colourless rod (EtOH), mp 159°C; ir (KBr, cm^{-1}): 3059 (m), 2954 (m), 2932 (m), 2866 (m), 1725 (s), 1587 (m), 1443 (m), 1278 (m), 1106 (m); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.39–1.41 (t, 3H, Me), 1.67–1.75 (m, 6H, 3xCH_2), 2.03 (s, 3H, Me), 3.65–3.80 (t, 4H, 2xN-CH_2), 4.33–4.40 (t, 2H, CH_2O), 8.56 (s, 1H, NH), 9.26 (s, 1H, NH^+); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 11.72 (Me), 13.92 (Me), 22.02 (CH_2), 27.56 (CH_2), 53.37 (CH_2), 59.92 (CH_2), 100.89 (4-C, Hetar), 146.50 (5-C, Hetar), 152.24 (3-C, Hetar), 161.91 (C=O); ms (El, 70 eV): *m/z* (%) = 42 (20), 55 (11), 84 (20), 97 (9), 136 (21), 151 (6), 162 (29), 190 (92), 208 (93), 237 (M^+, 100). *Anal*. Calcd. for $C_{12}H_{20}ClN_3O_2$ (273.76): C, 52.65; H, 7.36; N, 15.35. Found: C, 52.63; H, 7.39; N, 15.36.

3-Morpholino-4-ethoxycarbonyl-5-methyl-pyrazole (10c). *Hydrochloride*: From 1.61 g (10 mmol) of **2d**. To the mixture was added, after 10 min, 1 mL of ethanolic hydrochloric acid. After 1 h, the solvent was evaporated *in vacuo*. Yield: 2.04 g (74%), colourless needles (EtOH), mp 139°C; ir (KBr, cm^{-1}): 2970 (m), 2921 (m), 2864 (m), 2782 (m), 2762 (m), 2695 (m), 2581 (m), 1707 (s), 1587 (m), 1521 (m), 1464 (m), 1442 (m), 1332 (m), 1261 (m), 1116 (s); ^{1}H nmr ($CDCl_3$, 300 MHz): δ = 1.22–1.27 (t, 3H, Me), 2.36 (s, 3H, Me), 3.14–3.17 (t, 4H, 2xCH_2), 3.68–3.71 (t, 4H, 2xCH_2), 4.12–4.19 (t, 2H, CH_2-O), 8.08 (s, br, 1H, NH^+); ^{13}C nmr (DMSO-d_6, 50 MHz): δ = 12.34 (Me), 14.11 (Me), 50.34 (CH_2), 59.30 (CH_2), 65.65 (CH_2), 99.32 (4-C, Hetar), 146.35 (5-C, Hetar), 156.83 (3-C, Hetar), 162.54 (C=O); ms (El, 70 eV): *m/z* (%) = 36 (77), 60 (6), 79 (15), 108 (39), 136 (65), 151 (100), 166 (48), 196 (39), 208 (30), 239 (M^+, 91). *Anal*. Calcd. for $C_{11}H_{18}ClN_3O_3$ (275.73): C, 47.92; H, 6.58; N, 15.24. Found: C, 48.01; H, 6.5;7 N, 15.14.

3-Morpholino-4-acetyl-5-methyl-pyrazole (10d). *Hydrochloride*: 1.61 g (10 mmol) of morpholino-thiocarbonyl-hydrazine **1d** and 1.3 g (10 mmol) of α-chloro-acetylacetone in 5 mL of ethanol were refluxed for 5 min. Yield: 1.80 g (73%), colourless prisms (EtOH), mp 116°C; ir (KBr, cm^{-1}): 3229 (m), 3097 (m), 3053 (m), 2968 (m), 2921 (m), 1664 (s), 1627 (s), 1512 (s), 1475 (m), 1456 (m), 1441 (m), 1415 (m), 1118 (m); ^{13}C NMR (DMSO-d_6, 50 MHz): δ = 12.64 (Me), 29.13 (Me), 51.48 (CH_2), 65.79 (CH_2), 110.15 (4-C, Hetar), 144.90 (5-C, Hetar), 157.65 (3-C, Hetar), 192.10 (C=O); ms (El, 70 eV): *m/z* (%) = 28 (22), 43 (31), 67 (11), 79 (14), 108 (53), 123 (60), 136 (98), 166 (79), 178 (100), 209 (M^+, 62). *Anal*. Calcd. for $C_{10}H_{16}ClN_3O_2$ (245.71): C, 48.88; H, 6.56; N, 17.10. Found: C, 48.87; H, 6.56; N, 17.08.

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