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SYNTHESIS AND ANTITUMOR ACTIVITY OF NOVEL *N'*-(2-BENZYLTHIOBENZENESULFONYL)-1*H*-PYRAZOLE-1-AMIDINE DERIVATIVES

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Abstract- A series of *N'*-(2-benzylthio-4-chlorobenzenesulfonyl)-1*H*-pyrazole-1-amidines (**23-36**) were synthesized by the reaction of 3-amino-2-(benzenesulfonyl)guanidines (**18-22**) with adequate 1,3-diketones. The compounds **23, 24, 26, 30, 31, 34** and **35** were tested *in vitro* in the full NCI 60 cell panel. The most potent compound in the series (**26**) showed substantial activity toward some cell lines of leukemia and cancer cells of lung, colon, CNS, melanoma, renal, prostate and breast (GI_{50} in the range 2.30-9.47 μM).

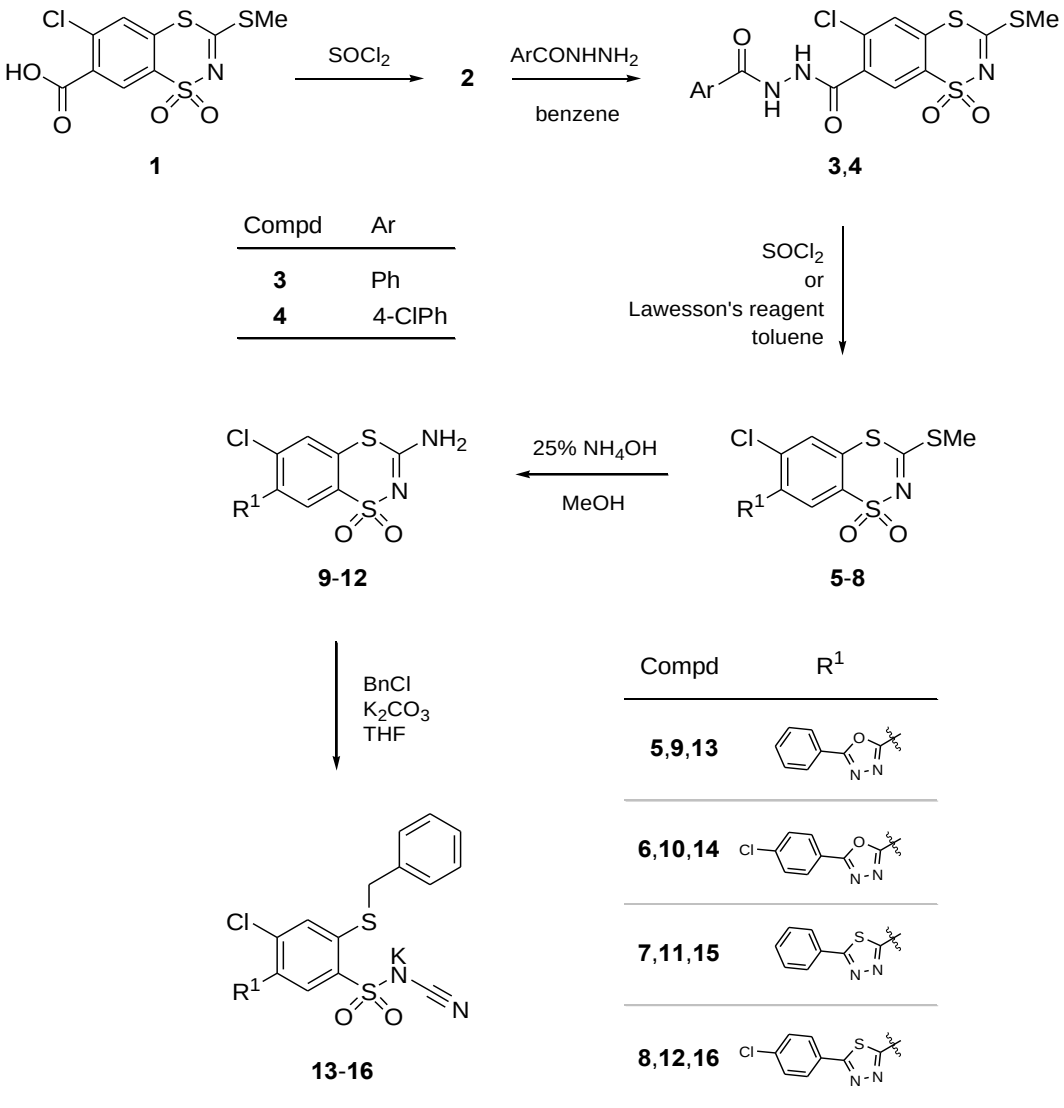
INTRODUCTION

A number of structurally novel sulfonamide derivatives have recently been reported to show substantial antitumor activity.[1,2]

Among them the 2-mercaptobenzenesulfonamides (MBSAs) have revealed much attention due to their substantial anticancer[3-5] or anti-HIV[6-8] activities. Recently, in the course of search for more potent analogues we synthesized a variety of 2-mercaptobenzenesulfonamide derivatives possessing heteroaromatic moieties substituting sulfonamide functionality.[9-12] Thus, we found that their anticancer properties strongly depend on the nature of the substituent attached to the sulfonamide nitrogen atom.[9-12] Currently, our interest turned to a pyrazole derivatives due to their broad spectrum of biological activity such as CDK4,[13] Aurora kinases,[14,15] p38-MAP kinase,[16,17] TGF-β[18] or HIV protease[19] inhibition. This prompted us to investigate the chemistry and biological activity of such compounds. Therefore in the present paper we elaborated an efficient method for the synthesis of novel *N'*-(2-benzylthio-4-chlorobenzenesulfonyl)-1*H*-pyrazole-1-amidine derivatives.

RESULTS AND DISCUSSION

The starting 7-(azol-2-yl)-1,1-dioxo-1,4,2-benzodithiazine derivatives (**5-8)** were synthesized in a three-step reaction, as outlined in Scheme 1. At first, starting 6-chloro-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylic acid (**1**)[20] was converted to the acid chloride (**2**)[21] followed by treatment with two molar equivalents of the appropriate benzhydrazide in dry benzene to give the corresponding *N,N′*-diaroylhydrazines (**3, 4**). The latter compounds were converted either to the 1,3,4-oxadiazoles (**5, 6**) in boiling thionyl chloride or to the corresponding 1,3,4-thiadiazole derivatives (**7, 8**) in the presence of one molar equivalent of Lawesson's reagent in toluene.

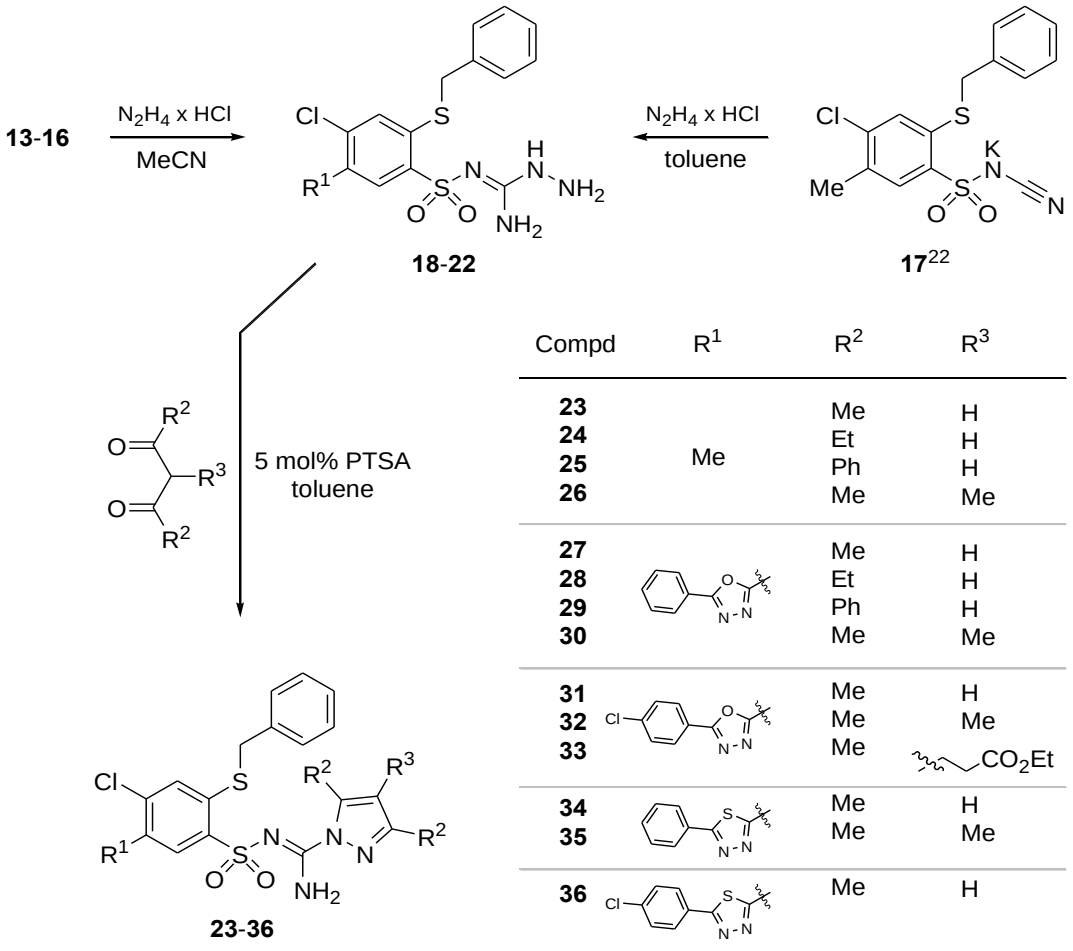


Scheme 1

3-Aminobenzodithiazines (**9-12**) were in turn obtained by the reaction of the corresponding 3-methylthio derivatives (**5-8**) with ammonium hydroxide in methanol at ambient temperature for 120 to 190 h (Scheme 1). Subsequent reaction of 3-aminobenzodithiazines (**9-12**) with an excess of anhydrous K_2CO_3 in dry

tetrahydrofuran in the presence of 1.2 molar equivalent of benzyl chloride furnished the desired novel *N*-(benzenesulfonyl)cyanamide potassium salts (**13-16**) in good (68-97%) yields.

The previously described method was employed for the synthesis of aminoguanidine (**18**)[22,23] (Scheme 2). Analogously were synthesized the new 3-amino-2-(benzylthio-4-chlorobenzenesulfonyl)guanidines (**19-22**). The syntheses of the target *N′*-(2-benzylthio-4-chlorobenzenesulfonyl)-1*H*-pyrazole-1-amidine derivatives (**23-36**) were achieved by reacting the corresponding aminoguanidines (**18-22**) with adequate 1,3-diketones in refluxing toluene in the presence of catalytic amount (0.05 equiv) of *p*-toluenesulfonic acid (PTSA).



Compd	R^1	R^2	R^3
23	Me	Me	H
24		Et	H
25		Ph	H
26		Me	Me
27		Me	H
28		Et	H
29		Ph	H
30		Me	Me
31		Me	H
32		Me	Me
33		Me	CO_2Et
34		Me	H
35		Me	Me
36		Me	H

Scheme 2

The structures of the compounds **3-16**, **19-22** and the final products **23-36** were confirmed by elemental analyses, IR and NMR spectroscopic data presented in experimental section. It is worth to note that the ^{1}H NMR spectra of the compounds **23-36** in DMSO solution exhibit two signals attributable to the protons of NH_2 group in the region δ = 7.88-8.46 and 8.59-9.31 ppm. This fact could be explained by the presence of intramolecular hydrogen bonds (*i.e.*, NH…N and NH…O).

Therefore, X-ray analysis of two representative final compounds **23** and **25** was undertaken (Figure 1). It showed very similar molecular features of the studied structures, resulting from two intramolecular hydrogen bonds (Table 2), namely N-H…N(*pyrazole*) and N-H…O(*sulfonyl*).

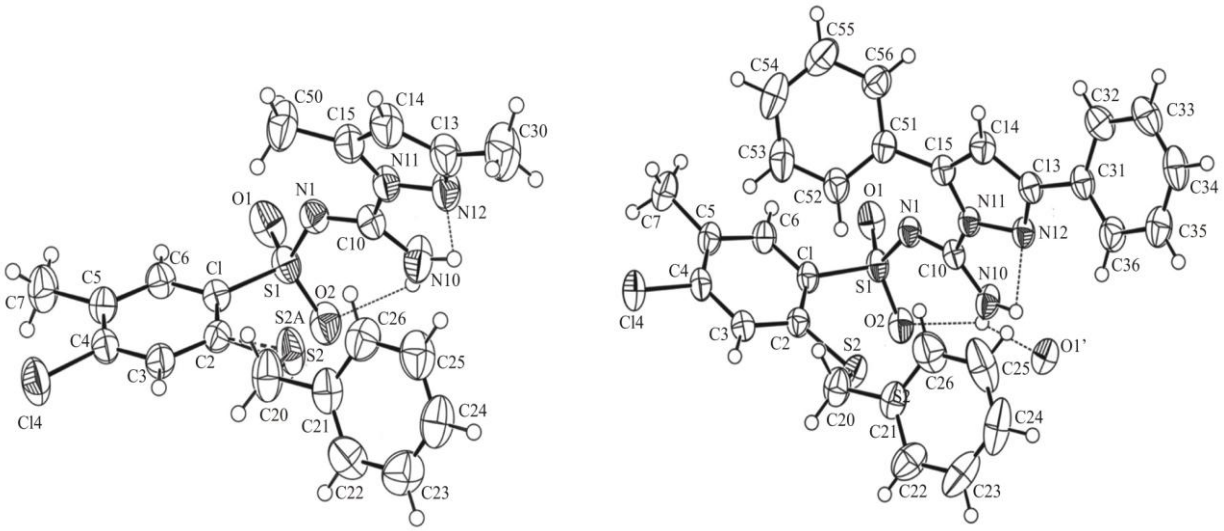


Figure 1. ORTEP drawing of the compounds **23** (left) and **25** (right) with 30% probability displacement ellipsoids for non-H atoms.

Table 1. Crystal data, data collection and refinement details of **23** and **25**

	23	**25**
Empirical formula	$C_{20}H_{21}ClN_4O_2S_2$	$C_{30}H_{25}ClN_4O_2S_2$
Molecular weight	448.98	573.11
Crystal size	0.5 x 0.41 x 0.34 mm	0.5 x 0.4 x 0.34 mm
Radiation	MoKα	MoKα
Wavelength	λ = 0.71073 Å	λ = 0.71073 Å
Crystal system	Monoclinic	Triclinic
Space group	P2(1)/n	P-1
Unit cell parameters	a = 9.161(3) Å	a = 10.8416(5) Å
	b = 12.789(4) Å	b = 11.3479(6) Å
	c = 18.649(6) Å	c = 11.4743(6) Å
	α = 90.0°	α = 82.154(1)°
	β = 99.273(6)°	β = 83.821(1)°
	γ = 90.0°	γ = 78.415(1)°
Volume , V	2156.2(12) $Å^3$	1365.28(12) $Å^3$
Molecular multiplicity, Z	4	2
Calculated density	1.383 g/cm^3	1.394 g/cm^3
Absorption coefficient, μ	0.395 mm^{-1}	0.329 mm^{-1}
2Θ range	56°	56°
Diffractometer	Bruker SMART APEX II	Bruker SMART APEX II
No. of reflections:		
measured	48111	31074
independent	5185	6473
observed ($I > 2\delta(I)$)	4625	5794
No. of parameters refined	275	353
R_1, R_{int}, wR_2	0.034 / 0.0382 / 0.1047	0.0353 / 0.0395 / 0.1088
S	1.03	1.01
$\Delta\rho_{min}$ / $\Delta\rho_{max}$	-0.34 / 0.26 $eÅ^{-3}$	-0.26 / 0.34 $eÅ^{-3}$

Table 2. Selected geometrical parameters in crystal structures of **23** and **25**

Parameter	**23**	**25**
Bond lengths (Å)		
S1—N1	1.6042(13)	1.6029(12)
N1—C10	1.2995(18)	1.3054(17)
C10—N10	1.326(2)	1.3176(18)
C10—N11	1.3934(19)	1.4083(17)
Bond angles (°)		
O1—S1—N1	109.72(7)	107.84(7)
O2—S1—N1	112.97(7)	114.60(6)
S1—N1—C10	123.16(10)	125.12(10)
N1—C10—N10	128.52(13)	129.84(13)
N1—C10—N11	116.92(12)	115.05(12)
C10—N11—N12	117.56(11)	117.24(11)
N10—C10—N11	114.54(12)	115.05(12)
Torsion angles (°)		
S1—N1—C10—N10	10.4(2)	12.7(2)
S1—N1—C10—N11	-170.95(10)	-170.19(10)
O2—S1—N1—C10	11.97(14)	0.73(15)
N12—N11—C10—N10	-2.69(18)	14.25(18)
Intramolecular hydrogen bonds (Å, °)		
N10—H10A···O2	126.2	126.7
H10A···O2	2.13	2.23
N10···O2	2.724(2)	2.831(2)
N10—H10B···N12	107.3	105.8
H10B···N12	2.19	2.25
N10···N12	2.583(2)	2.617(2)
Intermolecular hydrogen contact (Å, °)		
N10—H10A··· O1 [1-x, 1-y, -z]		133.6
H10A··· O1		2.61
N10··· O1		3.261(2)

The bonds define conformation of the *N*′-sulfonyl-1*H*-pyrazole-1-amidine fragments in **23** and **25** (Figure 1) In addition, an intermolecular weak hydrogen contact N-H…O(*sulfonyl*) is observed in structure **25** (Table 2 and Figure 1). It may be of some interest that no other crystal structure comprising *N*′-sulfonyl-1*H*-pyrazole-1-amidine frame has been studied until now.[24]

The compounds **23**, **24**, **26**, **30**, **31**, **34** and **35** were tested *in vitro* at the US National Cancer Institute (Bethesda, MD). Primary anticancer assay at concentration of 10^{-5} M in the full NCI 60 cell panel showed that compounds **30**, **31**, **34** and **35** were essentially inactive. Thus, it was interesting to find that replacement of methyl group in position 5 of benzene ring (R^1) with substituted five-membered heterocyclic rings decreased cytotoxicity considerably. On the other hand the compounds **23**, **24** and **26** showed some level of ability to inhibit the growth of human tumor cells. Therefore a secondary screening at five concentrations ranged from 10^{-8} to 10^{-4} M was performed for **23** and **26**. As shown in Table 3 the compounds **23** and **26**

exhibited reasonable anti-proliferative activity (GI_{50} <25 μM) over 23-29 cell lines. The most potent **26** showed substantial activity toward four to five cell lines of leukemia and cancer cells of lung and breast, and also one or two cell lines of colon, CNS, melanoma, renal and prostate (GI_{50} in the range 2.30-9.47 μM).

Table 3. Selected *in vitro* tumor growth inhibition data for compounds **23** and **26**.[a]

Tumor type	Cell line	GI_{50}[b] [μM]	
		23	**26**
Leukemia			
	RPMI-8226	5.93	2.90
	MOLT-4	6.18	3.52
	HL-60(TB)	6.75	2.30
	CCRF-CEM	9.15	4.49
	K-562	9.22	4.15
	SR	16.50	>100.00
Non-Small Cell Lung Cancer			
	HOP-92	3.82	3.17
	EKVX	6.08	5.38
	NCI-H522	7.78	>100.00
	NCI-H460	9.22	6.57
	NCI-H23	14.20	7.04
	A549/ATCC	31.30	14.00
Colon Cancer			
	HCT-116	7.20	38.50
	HCT-15	7.86	7.10
	HCC-2998	11.90	>100.00
	HT29	24.50	>100.00
	SW-620	24.80	72.70
	KM12	34.60	9.47
CNS Cancer			
	U251	16.80	7.47
	SNB-75	23.50	>100.00
	SF-295	34.30	7.99
Melanoma			
	UACC-62	12.40	>100.00
	M14	21.40	>100.00
	SK-MEL-5	40.70	5.65
Ovarian Cancer			
	OVCAR-3	22.60	46.40
	OVCAR-4	11.50	19.70
Renal Cancer			
	UO-31	5.18	4.57
	ACHN	24.40	>100.00
Prostate Cancer			
	PC-3	6.15	6.04
Breast Cancer			
	T-47D	4.21	3.14
	MCF7	13.30	5.12
	BR-549	17.80	-
	MDA-MB-435	21.30	3.23
	NCI/ADR-RES	87.10	9.22
	MDA-MB-468	-	12.10

[a] Data obtained from NCI's *in vitro* disease-oriented human tumor cell lines screen.[25]
[b] GI_{50} – molar concentration that inhibits 50% net cell growth.

EXPERIMENTAL

Melting points were determined with Boëtius apparatus and are uncorrected. The IR spectra were taken

using Thermo Mattson Satellite FTIR spectrophotometer, ^{1}H and ^{13}C NMR were taken with a Varian Gemini 200 MHz or Varian Unity Plus 500 MHz apparatus. Chemical shifts are reported in ppm (δ) and *J* values in Hz. The results of elemental analyses for C, H and N were in agreement with the calculated values within +/–0.4% range. The starting benzodithiazines **1**[20] and **2**,[21] *N*-(benzenesulfonyl)cyanamide potassium salt **17**[22] and aminoguanidine **18**[23] were synthesized according to the method described previously.

_N′_-(6-Chloro-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine-7-carbonyl)benzhydrazide (3)

To a stirred suspension of benzhydrazide (10 mmol, 1.362 g) in dry benzene (20 mL) the solution of 6-chloro-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine-7-carbonyl chloride (5 mmol, 1.711 g) in dry benzene (40 mL) was added dropwise at 5 °C. The resulting suspension was stirred at room temperature for 48 h and concentrated under reduced pressure to dryness. Water was added and the formed precipitate was filtered off and washed with water and 50% EtOH. Crude product was crystallized from EtOH. Yield: 1.888 g, 85%, mp 231-233 °C; IR (KBr) ν_{max} 3385, 3209, 2928, 1700, 1649, 1336, 1168 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.73 (s, 3H), 7.54-7.62 (m, 3H), 7.92-7.93 (m, 2H), 8.14 (s, 1H), 8.21 (s, 1H), 10.79 (s, 2H); *Anal.* Calcd for $C_{16}H_{12}ClN_3O_4S_3$: C, 43.48; H, 2.74; N, 9.51. Found: C, 43.31; H, 2.69; N, 9.35.

4-Chloro-_N′_-(6-chloro-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine-7-carbonyl)benzhydrazide (4)

To a stirred suspension of 4-chlorobenzhydrazide (10 mmol, 1.706 g) in dry benzene (20 mL) the solution of 6-chloro-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine-7-carbonyl chloride (5 mmol, 1.711 g) in dry benzene (40 mL) was added dropwise at 5 °C. The resulting suspension was stirred at room temperature for 48 h and concentrated under reduced pressure to dryness. Water was added and the formed precipitate was filtered off and washed with water and 50% EtOH. Crude product was crystallized from EtOH. Yield: 1.833 g, 80%, mp 258-260 °C; IR (KBr) ν_{max} 3379, 3216, 1685, 1654, 1323, 1161 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.50 (s, 3H), 7.62-7.64 (m, 2H), 7.95-7.97 (m, 2H), 8.13 (s, 1H), 8.21 (s, 1H), 10.86 (s, 2H); *Anal.* Calcd for $C_{16}H_{11}Cl_2N_3O_4S_3$: C, 40.34; H, 2.33; N, 8.82. Found: C, 40.11; H, 2.16; N, 8.73.

6-Chloro-7-(5-phenyl-1,3,4-oxadiazol-2-yl)-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine (5)

The suspension of **3** (5 mmol, 2.21 g) in thionyl chloride (25 mL) was stirred for 18 h at room temperature followed by refluxing for 2 h until the reaction mixture clarified. Solution obtained was concentrated under reduced pressure, and ice-water was slowly added. The crude product was granulated by stirring for 30 min, filtered off and washed with cold water, dried and purified by crystallization from DMF. Yield: 1.29 g, 62%, mp 254-255 °C; IR (KBr) ν_{max} 2917, 2841, 1605, 1464, 1337, 1178 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.75 (s, 3H), 7.66-7.69 (m, 3H), 8.15-8.16 (m, 2H), 8.36 (s, 1H), 8.71 (s, 1H); *Anal.* Calcd for

$C_{16}H_{10}ClN_3O_3S_3$: C, 45.33; H, 2.38; N, 9.91. Found: C, 45.22; H, 2.24; N, 9.84.

6-Chloro-7-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine (6)

The suspension of **4** (5 mmol, 2.38 g) in thionyl chloride (25 mL) was stirred for 18 h at room temperature followed by refluxing for 3 h until the reaction mixture clarified. Solution obtained was concentrated under reduced pressure, and ice-water was slowly added. The crude product was granulated by stirring for 30 min, filtered off and washed with cold water, dried and purified by crystallization from DMF to give pure 1,3,4-oxadiazoles. Yield: 1.97 g, 87%, mp 266-268 °C; IR (KBr) ν_{max} 2927, 1602, 1436, 1335, 1167 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.74 (s, 3H), 7.72-7.74 (m, 2H), 8.15-8.17 (m, 2H), 8.35 (s, 2H), 8.71 (s, 1H); *Anal.* Calcd for $C_{16}H_9Cl_2N4_3O_3S_3$: C, 41.93; H, 1.98; N, 9.17. Found: C, 41.88; H, 1.85; N, 9.06.

6-Chloro-7-(5-phenyl-1,3,4-thiadiazol-2-yl)-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine (7)

The suspension of **3** (5 mmol, 2.21 g) and Lawesson's reagent (5 mmol, 2.03 g) in dry toluene (75 mL) was stirred for 18 h at room temperature followed by refluxing for 2 h until the reaction mixture clarified. Solution obtained was kept at –20 °C for 2 h. The crystalline crude product was filtered off and washed with cold toluene and MeOH. Crystallization from *p*-dioxane gave pure title compound. Yield: 1.06 g, 48%, mp 246-248 °C; IR (KBr) ν_{max} 3082, 1578, 1532, 1501, 1454, 1334, 1165 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.76 (s, 3H), 7.62-7.64 (m, 3H), 8.11-8.12 (m, 2H), 8.37 (s, 1H), 8.84 (s, 1H); *Anal.* Calcd for $C_{16}H_{10}ClN_3O_2S_4$: C, 43.68; H, 2.29; N, 9.55. Found: C, 43.55; H, 2.18; N, 9.41.

6-Chloro-7-[5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl]-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine (8)

The suspension of **4** (5 mmol, 2.38 g) and Lawesson's reagent (5 mmol, 2.03 g) in dry toluene (75 mL) was stirred for 18 h at room temperature followed by refluxing for 2 h until the reaction mixture clarified. Solution obtained was kept at –20 °C for 2 h. The crystalline crude product was filtered off and washed with cold toluene and MeOH. Crystallization from DMF gave pure title compound. Yield: 1.47 g, 62%, mp 285-287 °C; IR (KBr) ν_{max} 3081, 2926, 1580, 1515, 1495, 1329, 1164 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.74 (s, 3H), 7.68-7.70 (m, 2H), 8.13-8.15 (m, 2H), 8.37 (s, 1H), 8.83 (s, 1H); *Anal.* Calcd for $C_{16}H_9Cl_2N_3O_2S_4$: C, 40.51; H, 1.91; N, 8.86. Found: C, 40.48; H, 1.86; N, 8.87.

3-Amino-6-chloro-1,1-dioxo-1,4,2-benzodithiazines (9-12). General procedure:

Suspension of the appropriate 3-methylthio derivative **5-8** (3 mmol) in MeOH (5 mL) was cooled to 0 °C and ammonium hydroxide solution (25%, 4 mmol, 0.27 g) was added dropwise. The suspension was stirred at room temperature (120-190 h) until MeSH ceased to evolve (CAUTION: due to a high toxicity, MeSH should be trapped into an aqueous NaOH solution). Precipitated almost pure product was filtered off and

crystallized from the appropriate solvent.

3-Amino-6-chloro-7-(5-phenyl-1,3,4-oxadiazol-2-yl)-1,1-dioxo-1,4,2-benzodithiazine (9)
Crystallization from 70% DMF/H_2O yielded: 0.849 g, 72%, mp 304-306 °C; IR (KBr) ν_{max} 3339, 3294, 3152, 1634, 1590, 1539, 1514, 1483, 1450 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.65-7.70 (m, 3H), 8.13-8.14 (m, 2H), 8.28 (s, 1H), 8.60 (s, 1H), 9.41 (br s, 2H); *Anal.* Calcd for $C_{15}H_9ClN_4O_3S_2$: C, 45.86; H, 2.31; N, 14.26. Found: C, 45.77; H, 2.21; N, 14.16.

3-Amino-6-chloro-7-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-1,4,2-benzodithiazine (10)
Crystallization from DMF yielded: 0.961 g, 75%, mp 301-303 °C; IR (KBr) ν_{max} 3368, 3287, 3155, 3083, 1628, 1605, 1588, 1510, 1482, 1347, 1316, 1168 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.70-7.74 (m, 2H), 8.12-8.17 (m, 2H), 8.28 (s, 1H), 8.59 (s, 1H), 9.40 (br s, 2H); *Anal.* Calcd for $C_{15}H_8Cl_2N_4O_3S_2$: C, 42.16; H, 1.89; N, 13.11. Found: C, 42.08; H, 1.81; N, 13.05.

3-Amino-6-chloro-7-(5-phenyl-1,3,4-thiadiazol-2-yl)-1,1-dioxo-1,4,2-benzodithiazine (11)
Crystallization from 70% DMF/H_2O yielded: 0.994 g, 81%, mp >320 °C; IR (KBr) ν_{max} 3355, 3290, 3138, 1631, 1584, 1554, 1357, 1308, 1166 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.60-7.63 (m, 3H), 8.07-8.12 (m, 2H), 8.27 (s, 1H), 8.74 (s, 1H), 9.38 (br s, 2H); *Anal.* Calcd for $C_{15}H_9ClN_4O_2S_3$: C, 44.06; H, 2.22; N, 13.70. Found: C, 43.97; H, 2.05; N, 13.64.

3-Amino-6-chloro-7-[5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl]-1,1-dioxo-1,4,2-benzodithiazine (12)
Crystallization from DMF yielded: 1.157 g, 87%, mp >320 °C; IR (KBr) ν_{max} 3295, 3082, 1582, 1534, 1516, 1495, 1343, 1329, 1165 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.69-7.70 (m, 2H), 8.14-8.15 (m, 2H), 8.38 (s, 1H), 8.84 (s, 1H), 9.40 (br s, 2H); *Anal.* Calcd for $C_{15}H_8Cl_2N_4O_2S_3$: C, 40.64; H, 1.82; N, 12.64. Found: C, 40.51; H, 1.77; N, 8.52.

***N*-(2-Benzylthio-4-chlorobenzenesulfonyl)cyanamide potassium salts (13-16). General procedure:**
Suspension of the appropriate 3-amino derivative **9-12** (2 mmol), anhydrous K_2CO_3 (10 mmol, 1.38 g) and benzyl chloride (2.17 mmol, 0.28 g) in dry THF (15 mL) was heated at reflux for 20-24 h, then cooled in ice-bath and filtered off. The crude product was suspended in 10 mL of water, heated gently to *ca.* 50 °C, and cooled with vigorous stirring until granular precipitate appeared. Filtering off and washing with cold water and diluted EtOH gave pure potassium salts.

***N*-[2-Benzylthio-4-chloro-5-(5-phenyl-1,3,4-oxadiazol-2-yl)benzenesulfonyl]cyanamide potassium salt**

(13)

Yield: 0.709 g, 68%, mp >320 °C; IR (KBr) ν_{max} 3061, 2924, 2170, 1583, 1556, 1526, 1492, 1450, 1297, 1143 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 4.45 (s, 2H), 7.30-7.42 (m, 3H), 7.49-7.52 (m, 2H), 7.63-7.70 (m, 4H), 8.06-8.11 (m, 2H), 8.48 (s, 1H); *Anal.* Calcd for $C_{22}H_{14}ClKN_4O_3S_2$: C, 50.71; H, 2.71; N, 10.75. Found: C, 50.63; H, 2.72; N, 10.71.

***N*-{2-Benzylthio-4-chloro-5-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]benzenesulfonyl}cyanamide potassium salt (14)**

Yield: 0.844 g, 76%, mp >320 °C; IR (KBr) ν_{max} 3086, 2167, 1585, 1543, 1524, 1483, 1293, 1140 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 4.46 (s, 2H), 7.31-7.33 (m, 1H), 7.37-7.40 (m, 2H), 7.50-7.52 (m, 2H), 7.71-7.74 (m, 3H), 8.09-8.11 (m, 2H), 8.49 (s, 1H); *Anal.*Calcd for $C_{22}H_{13}Cl_2KN_4O_3S_2$: C, 47.57; H, 2.36; N, 10.09. Found: C, 47.46; H, 2.29; N, 10.07.

***N*-[2-Benzylthio-4-chloro-5-(5-phenyl-1,3,4-thiadiazol-2-yl)benzenesulfonyl]cyanamide potassium salt (15)**

Yield: 0.838 g, 78%, mp 150-152 °C; IR (KBr) ν_{max} 3059, 2926, 2853, 2173, 1574, 1526, 1494, 1455, 1282, 1140 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 4.43 (s, 2H), 7.30-7.42 (m, 3H), 7.48-7.53 (m, 2H), 7.58-7.61 (m, 3H), 7.70 (s, 1H), 8.06-8.11 (m, 2H), 8.70 (s, 1H); *Anal.* Calcd for $C_{22}H_{14}ClKN_4O_2S_3$: C, 49.19; H, 2.63; N, 10.43. Found: C, 49.12; H, 2.45; N, 10.35.

***N*-{2-Benzylthio-4-chloro-5-[5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl]benzenesulfonyl}cyanamide potassium salt (16)**

Yield: 1.109 g, 97%, mp 237-239 °C; IR (KBr) ν_{max} 2924, 2178, 1626, 1580, 1527, 1497, 1357, 1280, 1138 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 4.42 (s, 2H), 7.28-7.30 (m, 1H), 7.35-7.38 (m, 2H), 7.48-7.49 (m, 2H), 7.64-7.65 (m, 2H), 7.68 (s, 1H), 8.08-8.10 (m, 2H), 8.70 (s, 1H); *Anal.* Calcd for $C_{22}H_{13}Cl_2KN_4O_2S_3$: C, 46.23; H, 2.29; N, 9.80. Found: C, 46.14; H, 2.18; N, 9.69.

3-Amino-2-(2-benzylthio-4-chlorobenzenesulfonyl)guanidines (19-22). General procedure:

Suspension of the appropriate potassium salt **13-16** (1 mmol) and hydrazine monohydrochloride (2 mmol, 0.137 g) in dry MeCN (10 mL) was stirred at reflux for 18-24 h. The precipitated white solid was filtered off and washed with H_2O (1 mL), diluted MeOH (1 mL) and MeCN (1 mL). Crystallization from DMF gave pure title compounds.

3-Amino-2-[2-benzylthio-4-chloro-5-(5-phenyl-1,3,4-oxadiazol-2-yl)benzenesulfonyl]guanidine (19)

Yield: 0.371 g, 72%, mp 278-280 °C; IR (KBr) ν_{max} 3467, 3355, 3213, 2934, 1655, 1620, 1603, 1589, 1554, 1483, 1275, 1119 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 4.47 (s, 2H), 4.55 (s, 2H), 7.08 (s, 2H), 7.31-7.33 (m, 1H), 7.37-7.40 (m, 2H), 7.50-7.51 (m, 2H), 7.64-7.69 (m, 3H), 7.73 (s, 1H), 8.10-8.12 (m, 2H), 8.54 (s, 1H), 8.58 (s, 1H); *Anal.* Calcd for $C_{22}H_{19}ClN_6O_3S_2$: C, 51.31; H, 3.72; N, 16.32. Found: C, 51.23; H, 3.68; N, 16.24.

3-Amino-2-{2-benzylthio-4-chloro-5-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]benzenesulfonyl}-guanidine (20)

Yield: 0.505 g, 92%, mp 238-239 °C; IR (KBr) ν_{max} 3435, 3362, 3322, 2931, 1652, 1610, 1584, 1482, 1281, 1136 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 4.47 (s, 2H), 4.55 (s, 2H), 7.08 (s, 2H), 7.31-7.32 (m, 1H), 7.37-7.40 (m, 2H), 7.49-7.51 (m, 2H), 7.72-7.74 (m, 3H), 8.10-8.12 (m, 2H), 8.54 (s, 1H), 8.58 (br s, 1H); *Anal*. Calcd for $C_{22}H_{18}Cl_2N_6O_3S_2$: C, 48.09; H, 3.30; N, 15.30. Found: C, 47.91; H, 3.22; N, 15.18.

3-Amino-2-[2-benzylthio-4-chloro-5-(5-phenyl-1,3,4-thiadiazol-2-yl)benzenesulfonyl]guanidine (21)

Yield: 0.435 g, 82%, mp 272-274 °C; IR (KBr) ν_{max} 3472, 3441, 3342, 3216, 1659, 1605, 1572, 1527, 1494, 1454, 1352, 1275, 1134 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 4.45 (s, 2H), 4.54 (s, 2H), 7.05 (s, 2H), 7.29-7.41 (m, 3H), 7.48-7.51 (m, 2H), 7.59-7.61 (m, 3H), 7.72 (s, 1H),8.05-8.09 (m, 2H), 8.55 (s, 1H), 8.74 (s, 1H); *Anal.* Calcd for $C_{22}H_{19}ClN_6O_2S_3$: C, 49.75; H, 3.61; N, 15.82. Found: C, 49.65; H, 3.51; N, 15.78.

3-Amino-2-{2-benzylthio-4-chloro-5-[5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl]benzenesulfonyl}-guanidine (22)

Yield: 0.452 g, 80%, mp 276-278 °C; IR (KBr) ν_{max} 3441, 2924, 2853, 1659, 1606, 1573, 1527, 1495, 1454, 1354, 1293, 1137 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 4.45 (s, 2H), 4.54 (s, 2H), 7.08 (s, 2H), 7.29-7.51 (m, 5H), 7.65-7.69 (m, 2H), 7.69 (s, 1H), 8.08-8.12 (m, 2H), 8.55 (br s, 1H), 8.74 (s, 1H); *Anal.* Calcd for $C_{22}H_{18}Cl_2N_6O_2S_3$: C, 46.72; H, 3.21; N, 14.86. Found: C, 46.64; H, 3.15; N, 14.71.

***N′*-(2-Benzylthio-4-chlorobenzenesulfonyl)-1*H*-pyrazole-1-amidines (23-36). General procedure:**

A mixture of the appropriate aminoguanidine **18-22** (1 mmol), adequate 1,3-diketone (1 mmol) and PTSA×H_2O (0.05 mmol, 0.01 g) in dry toluene (5 mL) was heated at reflux for 7-8 h. By-products were filtered out and the filtrate was left at –20 °C for crystallization. In some cases (**29** and **33**) mother liquor was evaporated to dryness and then purified by crystallization from MeCN.

***N′*-(2-Benzylthio-4-chloro-5-methylbenzenesulfonyl)-3,5-dimethyl-1*H*-pyrazole-1-amidine (23)**

Starting from **18** and 2,4-pentanedione (0.100 g) pure compound **23** was obtained after crystallization from MeCN (0.332 g, 74%), mp 168-170 °C; IR (KBr) ν_{max} 3451, 3334, 2981, 2925, 1637, 1580, 1522, 1496, 1346, 1324, 1289, 1129, 1109, 1075 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.20 (s, 3H), 2.31 (s, 3H), 2.33 (s, 3H), 4.33 (s, 2H), 6.20 (s, 1H), 7.19-7.22 (m, 5H), 7.58 (s, 1H), 7.88 (br s, 1H), 7.98 (s, 1H), 8.69 (br s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 13.68, 15.34, 19.19, 36.38, 112.10, 127.54, 128.22, 128.64, 129.13, 130.96, 132.59, 136.06, 136.33, 137.78, 138.02, 144.01, 151.45, 151.74; *Anal.* Calcd for $C_{20}H_{21}ClN_4O_2S_2$: C, 53.50; H, 4.71; N, 12.48. Found: C, 53.58; H, 4.82; N, 12.61.

***N′*-(2-Benzylthio-4-chloro-5-methylbenzenesulfonyl)-3,5-diethyl-1*H*-pyrazole-1-amidine (24)**

Starting from **18** and 3,5-heptanedione (0.128 g) pure compound **24** was obtained after crystallization from MeCN (0.367 g, 77%), mp 141-142 °C; IR (KBr) ν_{max} 3455, 3347, 2977, 2934, 1637, 1522, 1315, 1293, 1129 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 0.98 (t, J=7.4 Hz, 3H), 1.78 (t, J=7.6 Hz, 3H), 2.32 (s, 3H), 2.56 (q, J=7.6 Hz, 2H), 2.81 (q, J=7.4 Hz, 3H), 4.31 (s, 2H), 6.26 (s, 1H), 7.17-7.28 (m, 5H), 7.57 (s, 1H), 7.91 (br s, 1H), 7.99 (s, 1H), 8.63 (br s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 12.57, 12.78, 18.91, 21.04, 21.78, 36.11, 108.62, 127.25, 127.80, 128.36, 128.88, 130.75, 132.24, 135.96, 136.03, 137.52, 137.57, 149.90, 151.16, 156.93; *Anal.* Calcd for $C_{22}H_{25}ClN_4O_2S_2$: C, 55.39; H, 5.28; N, 11.74. Found: C, 55.46; H, 5.33; N, 12.12.

***N′*-(2-Benzylthio-4-chloro-5-methylbenzenesulfonyl)-3,5-diphenyl-1*H*-pyrazole-1-amidine (25)**

Starting from **18** and 1,1-dibenzoylmethane (0.224 g) pure compound **25** was obtained after crystallization from MeCN (0.201 g, 35%), mp 116-118 °C; IR (KBr) ν_{max} 3461, 3440, 3348, 3326, 2922, 2855, 1644, 1526, 1343, 1326, 1294, 1284, 1131 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.28 (s, 3H), 4.25 (s, 2H), 6.85-6.92 (m, 2H), 7.03-7.31 (m, 9H), 7.47-7.50 (m, 5H), 8.02-8.05 (m, 2H), 8.24 (br s, 1H), 9.18 (br s, 1H); *Anal.* Calcd for $C_{30}H_{25}ClN_4O_2S_2$: C, 62.87; H, 4.40; N, 9.78. Found: C, 62.78; H, 4.35; N, 9.74.

***N′*-(2-Benzylthio-4-chloro-5-methylbenzenesulfonyl)-3,4,5-trimethyl-1*H*-pyrazole-1-amidine (26)**

Starting from **18** and 3-methyl-2,4-pentanedione (0.114 g) pure compound **26** was obtained after crystallization from MeCN/EtOH (0.306 g, 66%), mp 110-111 °C; IR (KBr) ν_{max} 3473, 3361, 2921, 1622, 1522, 1323, 1136 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.86 (s, 3H), 2.15 (s, 3H), 2.21 (s, 3H), 2.31 (s, 3H), 4.31 (s, 2H), 7.16-7.21 (m, 5H), 7.58 (s, 1H), 7.80 (br s, 1H), 7.97 (s, 1H), 8.59 (br s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 7.55, 11.97, 13.20, 18.93, 36.10, 117.63, 127.22, 127.95, 128.33, 128.84, 130.67, 132.28, 135.74, 136.15, 137.45, 137.91, 139.22, 151.26, 151.70; *Anal.* Calcd for $C_{21}H_{23}ClN_4O_2S_2$: C, 54.48; H, 5.01; N, 12.10. Found: C, 54.56; H, 5.15; N, 12.34.

_N′_-[2-Benzylthio-4-chloro-5-(5-phenyl-1,3,4-oxadiazol-2-yl)benzenesulfonyl]-3,5-dimethyl-1_H_-pyrazole-1-amidine (27)

Starting from **19** and 2,4-pentanedione (0.100 g) pure compound **27** was obtained after crystallization from MeCN (0.521 g, 90%), mp 174-175 °C; IR (KBr) ν_{max} 3462, 3324, 2926, 1623, 1586, 1526, 1492, 1326, 1278, 1263, 1139, 1120 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.20 (s, 3H), 2.34 (s, 3H), 4.52 (s, 2H), 6.24 (s, 1H), 7.24-7.30 (m, 5H), 7.60-7.68 (m, 3H), 7.88 (s, 1H), 8.06-8.12 (m, 3H), 8.66 (s, 1H), 8.81 (br s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 13.68, 15.38, 35.97, 112.29, 118.35, 123.32, 127.07, 127.80, 128.81, 129.23, 129.29, 129.79, 130.56, 132.57, 135.63, 135.68, 137.93, 143.49, 144.12, 151.59, 151.97, 161.63, 164.61; *Anal.* Calcd for $C_{27}H_{23}ClN_6O_3S_2$: C, 56.00; H, 4.00; N, 14.51. Found: C, 55.96; H, 4.05; N, 14.42.

_N′_-[2-Benzylthio-4-chloro-5-(5-phenyl-1,3,4-oxadiazol-2-yl)benzenesulfonyl]-3,5-diethyl-1_H_-pyrazole-1-amidine (28)

Starting from **19** and 3,5-heptanedione (0.128 g) pure compound **28** was obtained after crystallization from MeCN (0.474 g, 78%), mp 92-93 °C; IR (KBr) ν_{max} 3427, 3356, 3321, 3083, 2971, 2922, 1633, 1605, 1584, 1538, 1492, 1313, 1298, 1263, 1147 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.01 (t, J=7.33 Hz, 3H), 1.19 (t, J=7.53 Hz, 3H), 2.59 (q, J=7,53 Hz, 2H), 2.86 (q, J=7.33 Hz, 2H), 4.51 (s, 2H), 6.30 (s, 1H), 7.24-7.34 (m, 5H), 7.62-7.68 (m, 3H), 7.87 (s, 1H), 8.08-8.13 (m, 3H), 8.67 (s, 1H), 8.75 (br s, 1H); *Anal.* Calcd for $C_{29}H_{27}ClN_6O_3S_2$: C, 57.37; H, 4.48; N, 13.84. Found: C, 57.28; H, 4.42; N, 13.68.

_N′_-[2-Benzylthio-4-chloro-5-(5-phenyl-1,3,4-oxadiazol-2-yl)benzenesulfonyl]-3,5-diphenyl-1_H_-pyrazole-1-amidine (29)

Starting from **19** and 1,1-dibenzoylmethane (0.224 g) pure compound **29** was obtained. Yield: 0.035 g (5%), mp 196-197 °C; IR (KBr) ν_{max} 3421, 3317, 2924, 1622, 1587, 1566, 1549, 1492, 1466, 1301, 1149 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 4.42 (s, 2H), 6.91-6.93 (m, 2H), 6.96-6.99 (m, 1H), 7.08-7.10 (m, 2H),7.16 (s, 1H), 7.22-7.27 (m, 3H), 7.38-7.39 (m, 2H), 7.44-7.47 (m, 1H), 7.49-7.52 (m, 2H), 7.68-7.71 (m, 3H), 7.76 (s, 1H), 8.04-8.06 (m, 2H), 8.12-8.14 (m, 2H), 8.18 (s, 1H), 8.46 (br s, 1H), 9.31 (br s, 1H); *Anal.* Calcd for $C_{37}H_{27}ClN_6O_3S_2$: C, 63.19; H, 3.87; N, 11.95. Found: C, 63.05; H, 3.81; N, 11.89.

_N′_-[2-Benzylthio-4-chloro-5-(5-phenyl-1,3,4-oxadiazol-2-yl)benzenesulfonyl]-3,4,5-trimethyl-1_H_-pyrazole-1-amidine (30)

Starting from **19** and 3-methyl-2,4-pentanedione (0.114 g) pure compound **30** was obtained after crystallization from MeCN (0.362 g, 61%), mp 139-140 °C; IR (KBr) ν_{max} 3435, 3329, 2925, 1631, 1586, 1528, 1327, 1144 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.89 (s, 3H), 2.17 (s, 3H), 2.25 (s, 3H), 4.51 (s,

2H), 7.26-7.29 (m, 5H), 7.64-7.67 (m, 3H), 7.88 (s, 1H), 7.97 (br s, 1H), 8.08-8.12 (m, 2H), 8.65 (br s, 1H), 8.72 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 7.84, 12.25, 13.49, 35.93, 118.11, 118.34, 123.32, 127.06, 127.76, 128.77, 129.21, 129.30, 129.79, 130.52, 132.57, 135.57, 135.77, 138.08, 139.56, 143.45, 151.66, 152.24, 161.64, 164.51; *Anal.* Calcd for $C_{28}H_{25}ClN_6O_3S_2$: C, 56.70; H, 4.25; N, 14.17. Found: C, 56.61; H, 4.12; N, 14.03.

N′-{2-Benzylthio-4-chloro-5-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]benzenesulfonyl}-3,5-dimethyl-1*H*-pyrazole-1-amidine (31)

Starting from **20** and 2,4-pentanedione (0.100 g) pure compound **31** was obtained after crystallization from MeCN (0.485 g, 79%), mp 201-202 °C; IR (KBr) ν_{max} 3464, 3350, 3090, 2925, 1620, 1584, 1525, 1482, 1327, 1142 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.21 (s, 3H), 2.34 (s, 3H), 4.53 (s, 2H), 6.25 (s, 1H), 7.27-7.29 (m, 3H), 7.32-7.34 (m, 2H), 7.73-7.74 (m, 2H), 7.89 (s, 1H), 8.06 (s, 1H), 8.11-8.13 (m, 2H), 8.67 (s, 1H), 8.82 (s, 1H); *Anal.* Calcd for $C_{27}H_{22}Cl_2N_6O_3S_2$: C, 52.86; H, 3.61; N, 13.70. Found: C, 52.72; H, 3.48; N, 13.58.

N′-{2-Benzylthio-4-chloro-5-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]benzenesulfonyl}-3,4,5-trimethyl-1*H*-pyrazole-1-amidine (32)

Starting from **20** and 3-methyl-2,4-pentanedione (0.114 g) pure compound **32** was obtained after crystallization from MeCN (0.414 g, 66%), mp 199-201 °C; IR (KBr) ν_{max} 3460, 3348, 2925, 1621, 1599, 1586, 1528, 1480, 1327, 1146 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.90 (s, 3H), 2.18 (s, 3H), 2.25 (s, 3H), 4.52 (s, 2H), 7.24-7.28 (m, 3H), 7.30-7.34 (m, 2H), 7.72-7.74 (m, 2H), 7.89 (s, 1H), 7.98 (br s, 1H), 8.11-8.13 (m, 2H), 8.66 (s, 1H), 8.82 (br s, 1H); *Anal.* Calcd for $C_{28}H_{24}Cl_2N_6O_3S_2$: C, 53.59; H, 3.85; N, 13.39. Found: C, 53.41; H, 3.69; N, 13.34.

N′-{2-Benzylthio-4-chloro-5-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]benzenesulfonyl}-4-(2-ethoxy-carbonylethyl)-3,5-dimethyl-1*H*-pyrazole-1-amidine (33)

Starting from **20** and ethyl 4-acetyl-5-oxohexanoate (0.200 g) pure compound **33** was obtained. Yield: 0.557 g (78%), mp 95-97 °C; IR (KBr) ν_{max} 3410, 3282, 2928, 1728, 1626, 1589, 1526, 1482, 1329, 1142 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.13 (t, *J*=6.83 Hz, 3H), 2.21 (s, 3H), 2.29 (s, 3H), 2.44 (t, *J*=7.33 Hz, 2H), 2.62 (t, *J*=7.33 Hz, 2H), 4.01 (q, *J*=6.83 Hz, 2H), 4.52 (s, 2H), 7.26-7.28 (m, 3H), 7.32-7.33 (m, 2H), 7.73-7.74 (m, 2H), 7.89 (s, 1H), 8.00 (br s, 1H), 8.12-8.14 (m, 2H), 8.67 (s, 1H), 8.76 (br s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 1.90, 12.22, 13.42, 14.27, 18.18, 33.88, 36.05, 60.21, 118.20,121.20, 122.21, 127.78, 128.79, 129.28, 129.31, 129.87, 130.56, 135.64, 137.31, 137.95, 140.38, 143.66, 151.60, 151.84,

161.77, 163.85, 172.25; *Anal.* Calcd for $C_{32}H_{30}Cl_2N_6O_5S_2$: C, 53.86; H, 4.24; N, 11.78. Found: C, 53.71; H, 4.10; N, 11.66.

_N′_-[2-Benzylthio-4-chloro-5-(5-phenyl-1,3,4-thiadiazol-2-yl)benzenesulfonyl]-3,5-dimethyl-1*H*-pyrazole-1-amidine (34)

Starting from **21** and 2,4-pentanedione (0.100 g) pure compound **34** was obtained after crystallization from acetone (0.411 g, 69%), mp 197-198 °C; IR (KBr) ν_{max} 3444, 3332, 2926, 1635, 1577, 1524, 1493, 1354, 1297, 1139 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.21 (s, 3H), 2.35 (s, 3H), 4.51 (s, 2H), 6.24 (s, 1H), 7.25-7.34 (m, 5H), 7.59-7.62 (m, 2H), 7.89 (s, 1H), 8.06-8.09 (m, 3H), 8.80 (s, 1H), 8.88 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 13.69, 15.37, 36.02, 112.27, 124.36, 127.80, 128.04, 128.81, 129.23, 129.45, 129.86, 130.11, 131.94, 135.32, 135.77, 138.22, 142.47, 144.10, 151.58, 151.96, 162.07, 169.43; *Anal.* Calcd for $C_{27}H_{23}ClN_6O_2S_3$: C, 54.49; H, 3.90; N, 14.12. Found: C, 54.35; H, 3.67; N, 14.04.

_N_-[2-Benzylthio-4-chloro-5-(5-phenyl-1,3,4-thiadiazol-2-yl)benzenesulfonyl]-3,4,5-trimethyl-1*H*-pyrazole-1-amidine (35)

Starting from **21** and 3-methyl-2,4-pentanedione (0.114 g) pure compound **35** was obtained after crystallization from acetone (0.347 g, 57%), mp 195-197 °C; IR (KBr) ν_{max} 3429, 3322, 2923, 1631, 1602, 1575, 1527, 1480, 1323, 1142 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.91 (s, 3H), 2.19 (s, 3H), 2.27 (s, 3H), 4.51 (s, 2H), 7.25-7.31 (m, 5H), 7.61-7.64 (m, 3H), 7.91 (s, 1H), 7.98 (br s, 1H), 8.08-8.11 (m, 2H), 8.72 (br s, 1H), 8.87 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 7.86, 12.26, 13.48, 35.98, 118.10, 124.36, 127.76, 128.05, 128.48, 128.78, 129.20, 129.36, 129.46, 129.88, 130.08, 131.96, 135.27, 135.87, 138.37, 138.55, 142.43, 151.65, 152.24, 162.10, 169.45; *Anal.* Calcd for $C_{28}H_{25}ClN_6O_2S_3$: C, 55.20; H, 4.14; N, 13.80. Found: C, 55.07; H, 3.98; N, 13.71.

_N′_-{2-Benzylthio-4-chloro-5-[5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl]benzenesulfonyl}-3,5-dimethyl-1*H*-pyrazole-1-amidine (36)

Starting from **22** and 2,4-pentanedione (0.100 g) pure compound **36** was obtained after crystallization from acetone (0.258 g, 41%), mp 194-196 °C; IR (KBr) ν_{max} 3439, 3331, 2925, 2853, 1638, 1578, 1525, 1492, 1332, 1297, 1134 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.19 (s, 3H), 2.33 (s, 3H), 4.49 (s, 2H), 6.22 (s, 1H), 7.25-7.32 (m, 3H), 7.65-7.67 (m, 2H), 7.87 (s, 1H), 8.04 (br s, 1H), 8.09-8.11 (m, 2H), 8.78 (br s, 1H), 8.85 (s, 1H); *Anal.* Calcd for $C_{27}H_{22}Cl_2N_6O_2S_3$: C, 51.51; H, 3.52; N, 13.35. Found: C, 51.42; H, 3.41; N, 13.18.

Crystallography. Selected monocrystals of **23** and **25** were measured with Mo radiation on Bruker SMART APEX diffractometer equipped with CCD area detector at room temperature. The structures were solved by direct methods and refined by full matrix least-square on F^2.[26] Though all hydrogen atoms were clearly visible at respective difference Fourier syntheses, they were placed at calculated positions and refined at fixed distances with isotropic thermal parameters. Respective crystal data, data collection and final refinement parameters for **23** and **25** are listed in Table 1.

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications No CCDC 80971 and CCDC 809720. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: C44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].

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