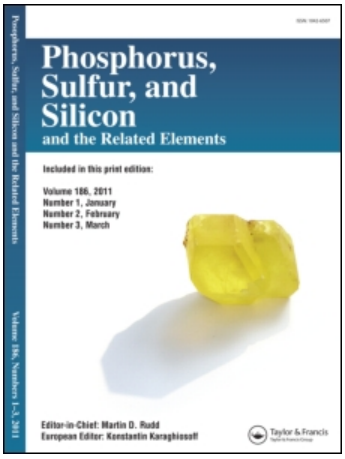

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW HETEROCYCLES BASED ON 3-METHYL-1-PHENYL-5-BENZENE SULFONAMIDO PYRAZOLE

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Treatment of 3-methyl 1-phenyl-5-amino pyrazole ***1*** *with 4-acetyl benzene sulfonyl chloride in pyridine gave the sulfonamide* ***2****. Condensation of* ***2*** *with aromatic aldehydes, semicarbazide, and thiosemicarbazide furnished the* α,β*-unsaturated ketones* ***3a–c****, the semicarbazone* ***4a*** *and the thiosemicarbazone* ***4b*** *respectively. Reaction of* ***3a–c*** *with hydrazine hydrate, phenyl hydrazine, hydroxylamine, thiourea afforded the pyrazoles* ***5a–f****, isoxazoles* ***6a–c****, and pyrimidinethiones* ***7a–c****. Reaction of* ***3a–c*** *with malononitrile in ethanol containing piperidine provided the pyran derivatives* ***8a–c****, while, when the reaction was carried out in boiling acetic acid in presence of ammonium acetate, the pyridine derivatives* ***9a–c*** *were formed. When* ***4a*** *reacted with thionyl chloride and with selenium dioxide, 1,2,3-thiadiazole and 1,2,3-selenadiazole* ***10****,* ***11*** *were formed respectively. Allowing* ***4b*** *to react with* α*-halocarbonyl compounds such as phenacyl bromide, chloroacetone, 2-bromomethyl propionate, chloroacetic acid, and bromo diethylmalonate afforded the thiazolines* ***12a,b*** *and thiazolidinones* ***13a–c*** *respectively.*

Keywords: Benzene sulfonamide; pyrazole

INTRODUCTION

The sulfonamides have been widely studied for their chemotherpeutic activity, their important role as antibacterial, insulin releasing, carbonic anhydrase inhibitory, antithyroid, antimalarial and antileprotic agents is recognized.[1–7]

Recently, certain sulfonamides have been reported as showing interesting antiinflammatory[8,9] and antitumor[10–12] activity. Some active

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sulfonamides as antibacterials are also known for their immunodifying effects.[13]

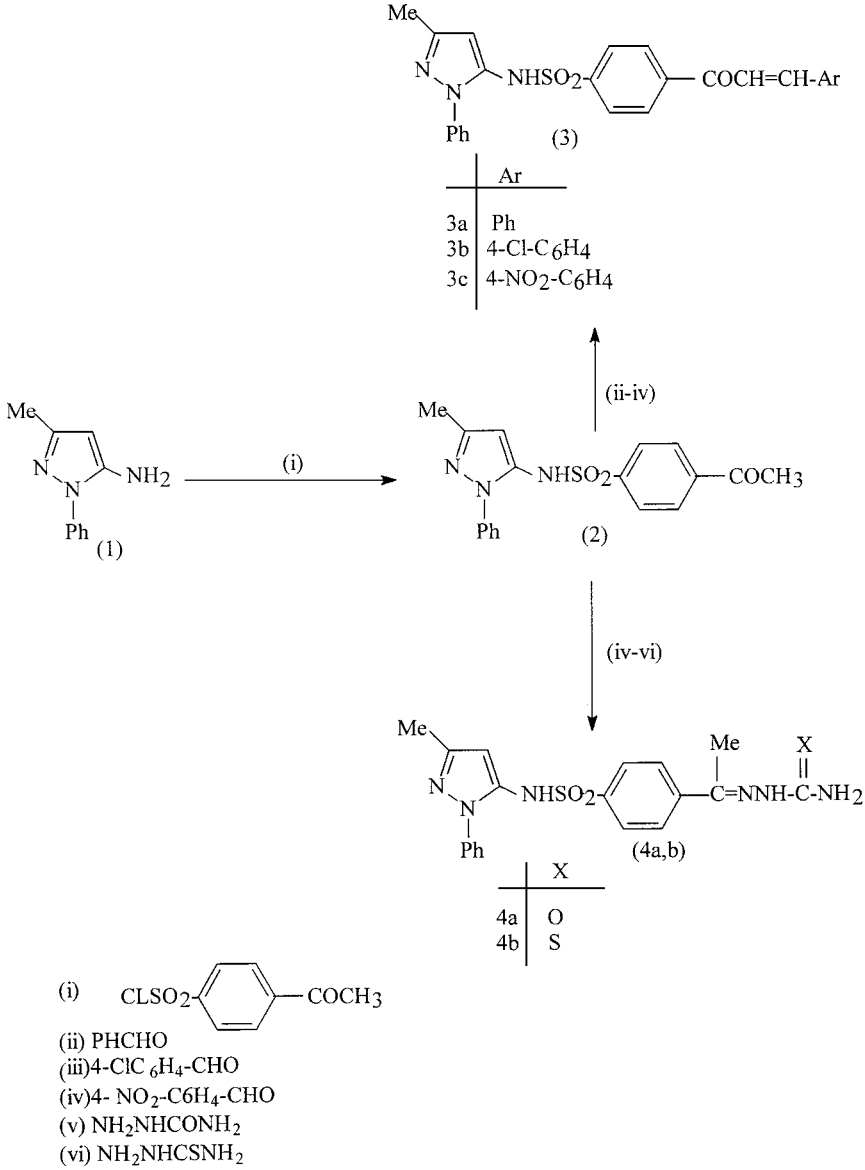
Pyrazole nucleus has received much attention during the last decades due to outstanding biological activities as antianxiety,[14] antipyretic, analgesic, antiinflammatory drugs,[15,16] and the antibacterial and antifungal properties.[17–22]

These observations encouraged us to continue our previous work[5,22] to synthesize new hetrocycles containing benzene sulfonamide moiety based on pyrazole ring, hoping to get compounds with enhanced potency. Some of the synthesized compounds were screened in vitro for antimicrobial activities.

DISCUSSION

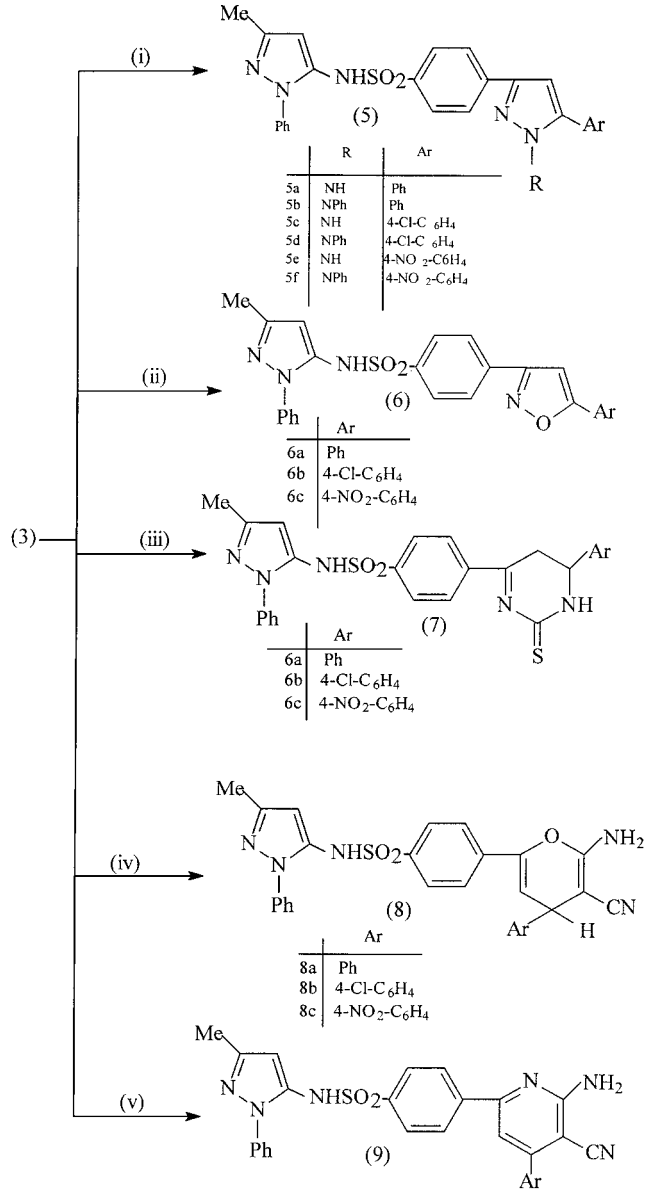
The reaction of 3-methyl-1-phenyl-5-amino pyrazole **1** with 4-acetyl benzene sulfonyl chloride led to the formation of 3-methyl-1-phenyl-5-(4′-acetyl)benzene sulfonamido pyrazole **2** (Scheme 1). Both the elemental and spectral data of compound **2** are in consistent. The ^{1}H NMR spectrum of 2, showed signals at 2.35 (s, 3H, CH_3), 3.15 (s, 3H, $COCH_3$), 7.1–8.4 (m, 10H, aromatic protons and pyrazole proton), and at 8.6 (s, 1H, SO_2NH); the IR spectrum displayed absorption bands at 3250, 1690, 1360, and 1145 cm^{-1}, which is characteristic for NH, CO and SO_{2asym}, SO_{2sym} groups.

The potency of the acetyl group of compound **2** was examined and used to synthesize new α,β-unsaturated ketones **3a–c**, semicarbazone **4a**, and thiosemicarbazone **4b** based on 3-methyl-1-phenyl-5-benzenesulfonamido pyrazole. Thus, the condensation of compound **2** with aromatic aldehydes, such as benzaldehyde, 4-chlorobenzaldehyde, and 4-nitrobenzaldehyde, using 10% aqueous sodium hydroxide produced the α,β-unsaturated ketons **3a–c** (Scheme 1). As well, the interaction of compound **2** with semicarbazide and with thiosemicarbazide afforded the semicarbazone and the thiosemicarbazone derivatives **4a**,**b** respectively. The structure of **3a–c** and **4a**,**b** were confirmed on the light of elemental and spectral data. Thus, for example, the ^{1}H NMR of compound **3a**, revealed signals at δ 2.50 (s, 3H, CH_3), 6.9–8.5 (m, 17H, Ar—H, pyrazole-H, ethylenic-H) and 8.7 (s, 1H, SO_2NH). The IR spectrum showed absorption bands at 3320, 1720, 1370, and 1150 cm^{-1} assigned for NH, CO, SO_{2asym}, and SO_{2sym} groups. The ^{1}H NMR of compound **4a** showed signals at δ 2.45 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 7.1–8.5 (m, 10H, Ar—H, pyrazole-H), 8.7 (s, 1H, SO_2NH), 9.1 (s, 1H, NH), 11.2 (s, 2H, NH_2). The IR spectrum revealed absorption bands at 3420–3270, 1365, 1140



SCHEME 1

cm^{-1} for (NH+ NH_2), for SO_{2asym} and SO_{2sym} groups. Compounds **3a–c** and **4a**,**b** were used as key intermediates in approach to synthesize a variety of heterocycles bearing sulfonamide moieties; thus, allowing compounds **3a–c** to interact with hydrazine hydrate, phenyl



	R	Ar
5a	NH	Ph
5b	NPh	Ph
5c	NH	4-Cl-C 6H4
5d	NPh	4-Cl-C 6H4
5e	NH	4-NO 2-C6H4
5f	NPh	4-NO 2-C6H4

	Ar
6a	Ph
6b	4-Cl-C_6H_4
6c	4-NO_2-C_6H_4

	Ar
6a	Ph
6b	4-Cl-C_6H_4
6c	4-NO_2-C_6H_4

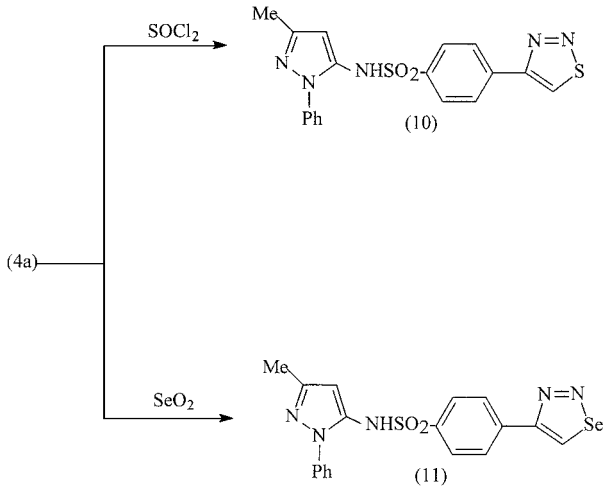
	Ar
8a	Ph
8b	4-Cl-C_6H_4
8c	4-NO_2-C_6H_4

	Ar
9a	Ph
9b	4-Cl-C_6H_4
9c	4-NO_2-C_6H_4

(i)= NH_2NHR (R = H, Ph) /EtOH
(ii)= $NH_2OH.HCl$ /EtOH, Sodium acetate
(iii)= $NHCSNH_2$/EtOH
(iv) = $CH_2(CN)_2$ /EtOH, piperidine
(v)= $CH_2(CN)_2/CH_3COONH_4$/AcOH

SCHEME 2

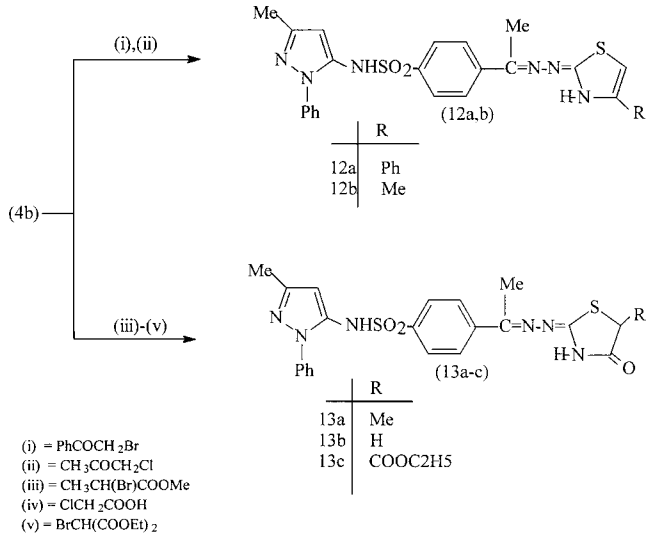
hydrazine, hydroxyl amine, and thiourea, the pyrazoles **5a–f**, isoxazoles **6a–c**, and pyrimidinethiones **7a–c** were produced (Scheme 2). As well, reaction of **3a–c** with malononitrile in ethanol containing piperidine provided the pyran derivatives **8a–c**, while when the reaction was carried out in the presence of ammonium acetate, the pyridine derivatives **9a–c** were formed (Scheme 2). The structures of the pyran derivatives **8a–c** and the pyridine derivatives **9a–c** have been investigated on the basis of elemental and spectral data, thus, for example the ^{1}H NMR of compound **8a** revealed the following signals at δ 2.5 (s, 3H, CH_3), 4.5 (s, 2H, NH_2), 5.0 (s, 1H, CH pyran), 7.2–8.3 (m, 15H, Ar—H, pyrazol-H), 8.6 (s, 1H, SO_2NH). The IR spectrum showed absorption band at 3420–3350, 3200, 2210 cm^{-1} for NH_2, NH, and CN groups. On the other hand, the ^{1}H NMR of compound **9a** revealed the following signals at δ 2.45 (s, 3H, CH_3), 6.7 (s, 2H, NH_2), 7.0–8.6 (m, 15H, Ar—H, Pyrazole-H), 8.8 (s, 1H, SO_2NH). The IR spectrum explore absorption bands at 3400–3290, 3250, 2220 cm^{-1} for NH_2, NH, and CN groups. Since 1,2,3-thiadiazole and 1,2,3-selenadiazoles are known by their antibacterial properties,[5,23–26] new members of these classes were synthesized by converting the semicarbazone **4a** by oxidative cyclization with thionyl chloride or selenium dioxide to give the 1,2,3-thiadiazole **10** and 1,2,3-selenadiazole **11** respectively (Scheme 3). The formation of the thiadiazole and selenadiazole **10**, **11** were confirmed by elemental analyses as well as by spectral data, thus the IR spectra are characterized by the absence of the carbonyl and amino bands of the semicarbazone **3**, while other bands were observed



SCHEME 3

and could be assigned to $\nu_{c\text{-}s}$ (750 cm^{-1}) for compound **10** and $\nu_{c\text{-}se\text{-}N}$ (840 cm^{-1}) for compound **11**.

The importance of compound **4b** as an interesting intermediate prompted us to explore its utility in the synthesis of new thiazolidine and thiazolidinone derivatives, thus allowing the thiosemicarbazone **4b** to react with some α-halocarbonyl compounds, namely phenacyl bromide, chloroacetone, 2-bromo methylpropionate, chloroacetic acid, and bromodimethyl malonate, in refluxing ethanol in the presence of sodium acetate, thiazoline, and thiazolidinone derivatives **12a**,**b** and **13a–c** were produced respectively. These reactions were assumed to proceed via S-alkylation followed by dehydration or loss of an alcohol molecule (Scheme 4).



SCHEME 4

ANTIMICROBIAL ACTIVITY

Fourteen compounds (**2**, **3a**,**b**, **4a**,**b**, **5b**, **5d**, **5f**, **7b**, **8b**, **9b**, **10**, **12a**, **13b**) were tested for their antimicrobial activity using gram positive and gram negative bacteria: *Bacillus cereus, Staphylococcus areus, Escherichia coli*, and *Micrococous leutea.* They were tested by filter paper disc method[27,28] at Assiut University by the aid of Prof. A. Moharam.

The result of the antimicrobial tests are summarized in Table I. All of the tested compounds were found to possess moderate to strong

TABLE I Antimicrobial Screen of the Synthesized Compounds[a]

Compd. no.	Bacellus cereus	Staphylococus aureus	Escherichia coli	Micrococcous leutea
2	12	12	11	—[b]
3a	12	11	11	—
3b	13	12	11	11
4a	11	11	—	—
4b	13	12	—	10
5b	11	11	—	—
5d	12	11	11	—
5f	12	11	—	—
7b	12	12	10	—
8b	10	—	—	—
9b	11	—	—	—
10	12	11	—	—
12a	13	12	11	11
13b	13	12	10	10
DMF	—	—	—	—

[a]Inhibition zones are measured in mm. The concentration used is 4×10^{-5} M. Control discs were performed with DMF (dimethylformamide) and no zones of inhibition were observed.

[b]— = resistant.

antimicrobial activity towards *B. cereus*. Also, all tested compounds except **8b** showed moderate antimicrobial activity against *S. areus.* Compounds **2**, **3a**, **3b**, **5d**, **7b**, **12a**, **13b** showed modreat activity against *E. coli* while the rest of the tested compounds showed resistant. Only four compounds, **3b**, **4b**, **12a**, **13b**, showed moderate activity against *M. leutea*, while the rest of the tested compounds showed no effect.

EXPERIMENTAL

All m.p.s are uncorrected and were determined on a Mel-Temp II apparatus. IR spectra were recorded on a Pye-Unicam SP3-100 spectrophotometer (ν_{max}. in cm^{-1}) using the KBr wafer technique, and ^1H NMR spectra were recorded on a 90 MHz Varian EM-390 NMR spectrophotometer in suitable solvents using TMS as an internal standard (chemical shifts in δ values). Elemental analyses were determined on a Perkin-Elmer 240 C microanalyser.

5-Amino-3-methyl-1-phenyl-pyrazole (1)

This compound was prepared according to the literature.[29]

3-Methyl-1-phenyl-5(4-acetyl)sulfonamidophenyl)-pyrazole (2)

4-Acetyl benzene sulphonyl chloride (0.01 mol) was added portionwise with shaking to **1** (0.01 mol) and dissolved in pyridine (25 ml). The reaction mixture was heated on a water bath for 2 h and then cooled and poured into ice water. The mixture was slightly acidifed with diluted HCl, and the precipitated solid was collected by filteration, washed with water, dried, and crystallized from, the proper solvent (cf. Tables II and III).

3-Methyl-1-phenyl-5(4(arylidine acetophenon-1-yl)sulfonamidophenyl)pyrazole (3a–c)

General Procedure

To a well stirred mixture of **2** (0.01 mol) and aromatic aldehydes, namely bezaldehyde, 4-chlorobenzaldehyde and 4-nitro benzaldehyde (0.01 mol) in ethanol (40 ml) an aqueous sodium hydoxide (10 ml, 10%), was added and the mixture was stirred at room temperature for 5–6 h. The precipitated solid was filtered washed with water, and crystallized from the proper solvent (cf. Tables II and III).

Condensation of 2 with semicarbazide: Formation of 3-methyl-1-phenyl-5(4-(acetyl semicarbazone-1-yl) benzene sulfonamido)pyrazole (4a)

A mixture of semicarbazide hydrochloride (0.01 mol) and sodium acetate (0.0 mol) dissolved in water (15 ml) was added to a solution of **2** (0.01 mol) and dissoved in ethanol (30 ml). The reaction mixture was heated under reflux for 2 h, evaporated to one half of its volume, and then poured into ice water. The solid pricipitate was filtered, washed with water, dried, and crystallized from the proper solvent (cf. Tables II and III).

Condensation of 2 with thiosemicarbazide: Formation of 3-methyl-1-phenyl-5(4-(acetyl thiosemicarbazone-1-yl) benzene sulfonamido)pyrazole (4b)

A mixture of **2** (0.01 mol) and thiosemicarbazide (0.01) in ethanol (30 ml) was heated under reflux for 2 h. The solid product was collected by filteration after cooling, washed with water, dried, and crystallized from the proper solvent (cf. Tables II and III).

TABLE II Physical and Analytical Data of the Synthesized Compounds

Compd. no.	M.P. (°C) (solvent)	Yield (%)	Mol. formula (mol. wt)	Elemental analyses required/found			
				C%	H%	N%	S%
2	135–137 (ethanol)	78	$C_{18}H_{17}N_3O_3S$ (355.4)	60.83 61.23	4.82 4.91	11.83 11.62	9.02 9.37
3a	192–193 (ethanol)	62	$C_{25}H_{21}N_3O_3S$ (443.5)	67.70 68.15	4.77 4.83	9.48 9.28	7.23 7.45
3b	210–212 (ethanol)	57	$C_{25}H_{20}N_3O_3SCl$ (477.9)	62.83 63.12	4.22 4.11	8.79 9.10	6.71 6.38
3c	235–237 (ethanol)	51	$C_{25}H_{20}N_4O_5S$ (488.5)	61.46 61.77	4.13 4.12	11.47 11.28	6.56 6.32
4a	260–262 (dioxan-water) (2:1)	58	$C_{19}H_{20}N_6O_3S$ (412.5)	55.32 55.65	4.89 5.10	20.38 20.58	7.77 7.65
4b	275–277 (dioxan-water) (3:1)	63	$C_{19}H_{20}N_6O_2S_2$ (428.5)	53.25 53.68	4.70 4.60	19.62 19.33	14.96 15.30
5a	248–250 (dioxan-water) (2:1)	52	$C_{25}H_{21}N_5O_2S$ (455.5)	65.92 66.36	4.65 4.87	15.38 15.15	7.04 6.88
5b	218–220 (ethanol)	61	$C_{31}H_{25}N_5O_2S$ (531.6)	70.04 70.43	4.74 4.48	13.18 13.45	6.03 5.88
5c	256–258 (ethanol)	48	$C_{25}H_{20}N_5O_2SCl$ (489.97)	61.28 62.56	4.11 4.12	14.30 14.35	6.54 6.23
5d	222–224 (ethanol)	54	$C_{31}H_{24}N_5O_2SCl$ (565.99)	65.77 66.15	4.27 4.37	12.37 12.12	5.66 5.52
5e	286–288 (ethanol)	42	$C_{25}H_{20}N_6O_4S$ (500.5)	59.99 60.42	4.03 4.13	16.80 16.62	6.41 6.21
5f	234–235 (dioxan-water) (2:1)	47	$C_{31}H_{24}N_6O_4S$ (576.6)	64.57 64.82	4.20 4.11	14.58 14.11	5.56 5.32
6a	186–188 (benzene)	41	$C_{25}H_{20}N_4O_3S$ (456.5)	65.77 66.12	4.42 4.23	12.28 12.08	7.02 6.76
6b	202–204 (ethanol)	37	$C_{25}H_{19}N_4O_3SCl$ (490.9)	61.16 61.48	3.90 3.80	11.42 11.12	6.53 6.18
6c	236–238 (ethanol)		$C_{25}H_{19}N_5O_5S$ (501.5)	59.87 60.22	3.82 3.93	13.97 13.63	6.39 6.11
7a	177–178 (ethanol)	62	$C_{26}H_{23}N_5O_2S_2$ (501.6)	62.25 62.55	4.62 4.87	13.96 13.77	12.78 12.54
7b	184–186 (ethanol)	53	$C_{26}H_{22}N_5O_2S_2Cl$ (536.1)	58.25 58.64	4.14 4.10	13.07 12.88	11.96 11.62
7c	220–222 (ethanol)		$C_{26}H_{22}N_6O_4S_2$ (546.6)	57.13 57.53	4.06 4.23	15.38 15.11	11.73 11.43
8a	250–252 ($CHCl_3$-pet. ether) (3:1)	51	$C_{28}H_{23}N_5O_3S$ (509.6)	65.99 66.37	4.55 4.77	13.75 13.66	6.29 5.89

(Continued on next page)

TABLE II Physical and Analytical Data of the Synthesized Compounds *(Continued)*

Compd. no.	M.P. (°C) (solvent)	Yield (%)	Mol. formula (mol. wt)	Elemental analyses required/found			
				C%	H%	N%	S%
8b	294–296 (dioxan)	43	$C_{28}H_{22}N_5O_3SCl$ (543.9)	61.83 62.23	4.08 4.16	12.88 12.67	5.89 5.55
8c	>300 (dioxan)	37	$C_{28}H_{22}N_6O_5S$ (554.6)	60.63 60.96	4.00 4.23	15.16 14.87	5.78 5.56
9a	>300 (acetic acid)	54	$C_{28}H_{22}N_6O_2S$ (506.6)	66.38 66.76	4.38 4.57	16.59 16.44	6.33 6.11
9b	>300 (acetic acid)	42	$C_{28}H_{21}N_6O_2SCl$ (540.99)	62.16 62.48	3.91 4.12	15.54 15.34	5.93 5.87
9c	>300 (acetic acid)	33	$C_{28}H_{21}N_7O_4S$ (551.6)	60.96 61.33	3.84 3.63	17.78 17.61	5.81 5.77
10	248–250 (ethanol)	41	$C_{18}H_{15}N_5O_2S_2$ (397.5)	54.38 54.78	3.80 3.81	17.62 17.54	16.13 16.22
11	217–218 (acetic acid)	28	$C_{18}H_{15}N_5O_2SSe$ (444.4)	48.64 48.87	3.40 3.48	15.76 15.37	7.21 6.97
12a	277–279 (dioxan)	63	$C_{27}H_{24}N_6O_2S_2$ (528.6)	61.35 61.74	4.58 4.66	15.90 15.65	12.13 12.14
12b	284–286 (ethanol)	55	$C_{22}H_{22}N_6O_2S_2$ (466.6)	56.63 56.78	4.75 4.68	18.02 17.85	13.74 13.43
13a	288–290 (dioxan)	52	$C_{22}H_{22}N_6O_3S_2$ (482.6)	54.75 54.87	4.60 4.76	17.42 17.13	13.29 13.11
13b	266–268 (acetone-water) (3:1)	58	$C_{21}H_{20}N_6O_3S_2$ (468.6)	53.82 53.87	4.30 4.76	17.92 17.63	13.68 13.27
13c	217–218 (ethanol)	49	$C_{24}H_{24}N_6O_5S_2$ (540.6)	53.32 53.78	4.48 4.41	15.55 15.23	11.86 11.65

Reaction of 3a–c with hydrazine hydrate and phenyl hydrazine: Formation of 3-methyl-1-phenyl-5(4(5-aryl-1-H(phenyl)-2-pyrazoline-3-yl)benzene sulfonamido) pyrazoles (5a–f)

General Procedure

A mixture of **3a–c** and hydrazine hydrate (excess, 1 ml, 80%) or phenyl hydrazine (0.006 mol) was heated gently without solvent for 15 min, then ethanol (25 ml) was added and the reaction mixture was heated under reflux for 6–8 h. After cooling, the product was collected by filteration, washed with water, dried, and crystallized from the proper solvent (cf. Tables II and III).

TABLE III Spectral Data of the Synthesized Compounds

Compd. no.	IR (ν) cm^{-1}	^1H NMR (δ) ppm
2	3250 (NH), 1690 (CO), 1360 ($SO_{2asym.}$), 1145 (SO_{2sym})	($CDCl_3$): 2.35 (s, 3H, CH_3), 3.15 (s, 3H, $COCH_3$), 7.1–8.4 (m, 10H, Ar-H + pyrazole-H), 8.6 (s, 1H, SO_2NH)
3a	3320 (NH), 1720 (CO), 1370 ($SO_{2asym.}$), 1150 (SO_{2sym})	(d_6-DMSO): 2.50 (s, 3H, CH_3), 6.9–8.5 (m, 17H, Ar-H + pyrazole-H + ethylenic-H), 8.7 (s, 1H, SO_2NH)
3b	3300 (NH), 1710 (CO), 1350 ($SO_{2asym.}$), 1140 (SO_{2sym})	(d_6-DMSO): 2.60 (s, 3H, CH_3), 7.1–8.2 (m, 16H, Ar-H + pyrazole-H + ethylenic-H), 8.4 (s, 1H, SO_2NH)
3c	3280 (NH), 1700 (CO), 1340 ($SO_{2asym.}$), 1130 (SO_{2sym})	(d_6-DMSO): 2.40 (s, 3H, CH_3), 6.8–8.0 (m, 16H, Ar-H + pyrazole-H + ethylenic-H), 8.1 (s, 1H, SO_2NH)
4a	3420-3270 ($2NH + NH_2$), 1700 (CO),1340 ($SO_{2asym.}$), 1130 (SO_{2sym})	(d_6-DMSO): 2.45 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 7.1–8.5 (m, 16H, Ar-H + pyrazole-H), 8.7 (s, 1H, SO_2NH), 9.1 (s, 1H, NH)
4b	3380-3260 ($2NH + NH_2$), 1340 ($SO_{2asym.}$), 1130 (SO_{2sym})	(d_6-DMSO): 2.50 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 6.9–8.1 (m, 10H,Ar-H + pyrazole-H), 8.3 (s, 1H, SO_2NH), 9.5 (s, 1H, NH), 11.5 ($_S$,2H, NH_2)
5a	3320, 3300 (2NH), 1350 ($SO_{2asym.}$), 1140 (SO_{2sym})	(d_6-DMSO): 2.45 (s, 3H, CH_3), 7.0–8.2 (m, 16H, Ar-H + pyrazole-H), 8.5 (s, 1H, SO_2NH), 9.2 (s, 1H, NH)
5b	3310 (NH),1360 ($SO_{2asym.}$), 1160 (SO_{2sym})	(d_6-DMSO): 2.55 (s, 3H, CH_3), 7.1–8.3 (m, 21H, Ar-H + 2pyrazole-H), 8.4 (s, 1H, SO_2NH)
5c	3330, 3280 (2NH), 1370 ($SO_{2asym.}$), 1160 (SO_{2sym})	(d_6-DMSO): 2.60 (s, 3H, CH_3), 7.2–8.1 (m, 15H, Ar-H + 2pyrazole-H), 8.3 (s, 1H, SO_2NH), 8.7 (s, 1H, NH)
5d	3320, 3290 (2NH),1350 (SO_{2asy}) 1135 (SO_{2sym})	(d_6-DMSO): 2.50 (s, 3H, CH_3), 7.3–8.2 (m, 20H, Ar-H + 2pyrazole-H), 8.4 (s, 1H, SO_2NH)
5e	3330 (NH), 1370 ($SO_{2asym.}$), 1135 (SO_{2sym})	(d_6-DMSO): 2.40 (s, 3H, CH_3), 7.1–8.2 (m, 15H, Ar-H + 2pyrazole-H), 8.3 (s, 1H, SO_2NH), 9.1 (s, 1H, NH)
5f	3330 (NH), 1370 ($SO_{2asym.}$), 1135 (SO_{2sym})	(d_6-DMSO): 2.30 (s, 3H, CH_3), 6.9–8.0 (m, 21H, Ar-H + 2pyrazole-H), 8.1 (s, 1H, SO_2NH), 9.1 (s, 1H, NH)
6a	3250 (NH), 1365 ($SO_{2asym.}$), 1130 (SO_{2sym})	(d_6-DMSO): 2.50 (s, 3H, CH_3), 6.9–8.4 (m, 16H, Ar-H + pyrazole-H + isoxazole-H), 8.5 (s, 1H, SO_2NH)

(Continued on next page)

TABLE III Spectral Data of the Synthesized Compounds. *(Continued)*

Compd. no.	IR (ν) cm^{-1}	^1H NMR (δ) ppm
6b	3250 (NH), 1355 ($SO_{2asym.}$), 1145 (SO_{2sym})	(d_6-DMSO): 2.45 (s, 3H, CH_3), 7.0–8.3 (m, 15H, Ar-H + pyrazole-H + isoxazole-H), 8.7 (s, 1H, SO_2NH)
6c	3150 (NH), 1360 ($SO_{2asym.}$), 1140 (SO_{2sym})	(d_6-DMSO): 2.30 (s, 3H, CH_3), 7.1–8.2 (m, 15H, Ar-H + pyrazole-H + isoxazole-H), 8.4 (s, 1H, SO_2NH)
7a	3400,3350 (2NH), 1345 (SO_{2asy}) 1135 (SO_{2sym})	(d_6-DMSO): 2.40 (s, 3H, CH_3), 4.2 (d, 2H, CH_2), 5.3 (t, 1H, CH), 7.2–8.2 (m, 15H, Ar-H),8.6 (s, 1H, SO_2NH), 9.1 (s, 1H, NH)
7b	3370,3320 (2NH), 1355 (SO_{2asy}) 1135 (SO_{2sym})	(d_6-DMSO): 2.35 (s, 3H, CH_3), 4.0 (d, 2H, CH_2), 4.9 (t, 1H, CH), 6.9–8.2 (m, 14H, Ar-H), 8.3 (s, 1H, SO_2NH), 9.1 (s, 1H, NH)
7c	3330,3350 (2NH), 1360 (SO_{2asy}) 1140 (SO_{2sym})	(d_6-DMSO): 2.30 (s, 3H, CH_3), 3.9 (d, 2H, CH_2), 4.8 (m, 1H, CH), 7.1–8.3 (m, 14H, Ar-H), 8.6 (s, 1H, SO_2NH), 9.5 (s, 1H, NH)
8a	3420,3350 (NH_2), 3200 (NH), 2210 (CN) 1320 (SO_{2asym}), 1130 (SO_{2sym})	(d_6-DMSO): 2.50 (s, 3H, CH_3), 4.50 (s, 2H, NH_2), 5.0–5.2 (m, 2H, pyran-H), 7.2–8.3 (m, 15H, Ar-H + pyrazole-H), 8.6 (s, 1H, SO_2NH)
8b	3390,3370 (NH_2), 3300 (NH), 2220 (CN),1350 ($SO_{2asym.}$), 1140 (SO_{2sym})	(d_6-DMSO): 2.40 (s, 3H, CH_3), 4.4 (s, 2H, NH_2), 4.9–5.1 (m, 2H, pyran-I) 7.1–8.2 (m, 14H, Ar-H + pyrazole-H), 8.5 (s, 1H, SO_2NH)
8c	3360,3340 (NH_2), 3300 (NH), 1370 ($SO_{2asym.}$),1150 (SO_{2sym})	(d_6-DMSO): 2.30 (s, 3H, CH_3),4.3 (s, 2H, NH_2), 4.8 (s, 1H, pyran-H), 7.2–8.2 (m, 16H, Ar-H + pyrazole-H), 8.6 (s, 1H, SO_2NH)
9a	3400,3290 (NH_2), 3250 (NH), 2220 (CN), 1370 ($SO_{2asym.}$), 1150 (SO_{2sym})	(d_6-DMSO): 2.45 (s, 3H, CH_3), 6.7 (s, 2H, NH_2) 7.0–8.6 (m, 15H, Ar-H + pyrazole-H + pyridine-H), 8.8 (s, 1H, SO_2NH)
9b	3390,3280 (NH_2), 3190 (NH), 2220 (CN), 1355 ($SO_{2asym.}$), 1140 (SO_{2sym})	(d_6-DMSO): 2.35 (s, 3H, CH_3), 6.2 (s, 2H, NH_2), 6.9–8.5 (m, 15H, Ar-H + pyrazole-H + pyridine-H), 8.7 (s, 1H, SO_2NH)
9c	3360-3250 (NH_2), 3150 (NH), 2220 (CN), 1365 ($SO_{2asym.}$), 1130 (SO_{2sym})	(d_6-DMSO): 2.30 (s, 3H, CH_3), 6.1 (s, 2H, NH_2), 7.0–8.4(m, 15H, Ar-H + pyrazole-H + pyridine-H), 8.7 (s, 1H, SO_2NH)

10	3330 (NH), 1370 ($SO_{2asym.}$), 1130 (SO_{2sym}), 750 (C—S—N)	(d_6-DMSO): 2.50 (s, 3H, CH_3), 7.2–8.4 (m, 11H, Ar-H + pyrazole-H + thiadiazolw-H), 8.7 (s, 1H, SO_2NH)
11	3310 (NH), 1365 ($SO_{2asym.}$), 1140 (SO_{2sym})	(d_6-DMSO): 2.40 (s, 3H, CH_3), 7.2–8.4 (m, 11H, Ar-H + pyrazole-H + selenadiazole-H), 8.6 (s, 1H, SO_2NH)
12a	3360,3320 (2NH), 1360 ($SO_{2asym.}$), 1125 (SO_{2sym}), 840 (C—Se—N)	(d_6-DMSO): 2.40 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 7.2–8.5 (m, 16H, Ar-H + pyrazole-H + thiazole-H),8.6 (s, 1H, SO_2NH), 9.8 (s, 1H, NH)
12b	3350,3330 (2NH),1355 ($SO_{2asym.}$),1130 (SO_{2sym})	(d_6-DMSO): 2.35 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 7.1–8.4 (m, 11H, Ar-H + pyrazole-H + thiazole-H), 8.5 (s, 1H, SO_2NH) 10.2 (s, 1H, NH)
13a	3350,3250 (2NH), 1690 (CO) 1370 ($SO_{2asym.}$), 1140 (SO_{2sym})	(d_6-DMSO): 2.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.2–8.4 (m, 10H, Ar-H + pyrazole-H), 8.6 (s, 1H, SO_2NH), 9.1 (s, 1H, NH)
13b	3380,3220 (2NH), 1700 (CO) 1360 ($SO_{2asym.}$), 1130 (SO_{2sym})	(d_6-DMSO): 2.35 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.95 (s,2H, CH_2), 7.2–8.4 (m, 10H,Ar-H + pyrazole-H), 8.6 (s, 1H, SO_2NH). 10.2 (s, 1H, NH)
13c	3400,3220 (2NH), 1740,1710 (2CO)1350 ($SO_{2asym.}$), 1140 (SO_{2sym})	(d_6-DMSO): 1.1–1.3 (t, 3H, CH_2—CH_3), 2.4 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 3.9–4.2 (q, 2H, CH_2—CH_3), 7.1–8.4 (m, 10H, Ar-H + pyrazole-H), 8.5 (s, 1H, $SONH_2$), 10.5 (s, 1H, NH)

Reaction of 3a–c with hydroxyl amine: Formation of 3-methyl-1-phenyl-5-(4-(5-aryl isoxazol-3-yl)benzen sulfonamido)pyrazoles (6a–c)

General Procedure

To a solution of **3a–c** (0.005 mol) in ethanol (25 ml), an aqueous solution (10 ml, containing hydroxyl amine hydrochloride (0.006 mol), and sodium acetate (0.008 mol) was added. The reaction mixture was then heated under reflux for 3–5 h. After cooling, the product was filtered off, washed with water, dried, and crystallized from the proper solvent (cf. Tables II and III).

Reaction of 3a–c with thiourea: Formation of 3-methyl-1-phenyl-5-(4-(6-aryl-pyrimidine-2-thione-4-yl) benzene sulfonamido)pyrazoles (7a–c)

General Procedure

Equimolar amounts (0.005 mol) of **3a–c** and thiourea were dissolved in ethanol (25 ml). To this solution, alcoholic KOH (5 ml, 25%) was added and the reaction mixture was heated under reflux for 6–8 h. The reaction mixture was cooled, poured into water, and neutralized with HCl. The product was filtered off, washed with water, dried, and crystallized from the proper solvent (cf. Tables II and III).

Reaction of 3a–c with malononitrile in ethanol/ piperidine: Formation of 3-methyl-1-phenyl-5-(4-(2-amino-4-aryl-3-cyano pyran-6-yl) benzene sulfonamido)pyrazole (8a–c)

General Procedure

A mixture of **3a–c** (0.005 mol) and malononitrile (0.005 mol) in ethanol (25 ml) containing piperidine (few drops) was heated under reflux for 4–7 h. After cooling, the product was filtered off, washed with water, dried, and crystallized from the proper solvent (cf. Tables II and III).

Reaction of 3a–c with malononitrile in acetic acid/ammonium acetate: Formation of 3-methyl-1-phenyl-5-(4-(2-amino-4-aryl-3-cyanopyridin-6-yl)benzene sulfonamido) pyrazoles (9a–c)

General Procedure

A mixture of **3a–c** (0.005 mol), malononitrile (0.005 mol), and ammonium acetate (0.01 mol) in acetic acid (20 ml) was heated under reflux

for 6–8 h. After cooling, the reaction mixture was poured into cold water, the product was filtered off, washed with water, dried, and crystallized from the proper solvent (cf. Tables II and III).

Reaction of the semicarbazone 4a with thionyl chloride: Formation of 3-methyl-1-phenyl-5-(4-(1,2,3-thiadiazole-4-yl) benzene sulfonamido) pyrazole (10)

Thionyl chloride (10 ml) was gradually added to the semicarbazone derivative **4a** (0.005 mol) at ice bath temperature. The reaction mixture was removed from the ice bath and heated on a water bath for 3 h. Chloroform (50 ml) was then added and the reaction mixture was decomposed with ice-cold saturated sodium carbonate solution and separated. The organic layer was washed with water and dried. After evaporation of the solvent, the residue was recrystallized from the proper solvent (cf. Tables II and III).

Reaction of the semicarbazone 4a with selenium dioxide: Formation of 3-methyl-1-phenyl-5-(4(4-(1,2,3-selenadiazole-4-yl) benzene sulfonamido) pyrazole (11)

To a boiling stirred solution of the semicarbazone **4a** (0.005 mol) in acetic acid (20 ml), selenium dioxide (0.005 mol) was added portionwise. The reaction mixture was filtered twice while hot. The cold filtrate was poured into ice water and the precipitate was filtered, washed with water, dried, and crystallized from the proper solvent (cf. Tables II and III).

Reaction of the thiosemicarbazone 4b with α-halocarbonyl compounds and α-haloesters: Formation of the thiazolidines 12a,b and the thiazolidinones (13a–c)

General Procedure

A mixture of **4b** (0.005 mol), α-halocarbonyl compounds or α-haloesters (0.005 mol), namely, phenacyl bromide, chloroacetone, α-bromo methylpropionate, chloroacetic acid, and bromo diethylmalonate, and sodium acetate (0.01 mol) in ethanol (30 ml) was heated under reflux for 6–8 h. After cooling, the precipitate was filtered, washed with water, dried, and crystallized from the proper solvent (cf. Tables II and III).

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