# Preparation and Antidiabetic Activity of New Substituted 3,5-Diarylpyrazolesulfonylurea Derivatives II: Structure–Activity Relationship

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**Abstract** □ Four series of substituted *p*-(3,5-diaryl-2-pyrazoline-1) benzenesulfonylurea and thiourea derivatives, along with their corresponding substituted *p*-(3,5-diarylpyrazole-1) benzenesulfonylurea and thiourea derivatives, were prepared for evaluation as hypoglycemic agents. Preliminary biological testing revealed that the new compounds possess potent hypoglycemic activity.

It has been reported that 3,5-dimethylpyrazoles possess hypoglycemic activities as great as 100 times that of tolbutamide in glucose-primed intact rats.[1–5] Studies have been conducted on the synthesis of new 3,5-disubstituted pyrazoles.[6–12] In continuation of our previous work,[8–12] many new substituted 3,5-diaryl-2-pyrazolinesulfonylurea derivatives and their corresponding pyrazole derivatives were prepared.

In light of the biological data presented here and published previously, a possible structure–activity relationship for antidiabetic activity may result.

Four series of *p*-[5-(*p*-methylphenyl)-3-phenyl-2-pyrazolin-1-yl]-, *p*-[5-(*p*-chlorophenyl)-3-phenyl-2-pyrazolin-1-yl]-, *p*-[5-(*p*-bromophenyl)-3-phenyl-2-pyrazolin-1-yl]-, and *p*-[5-phenyl-3-(*p*-methylphenyl)-2-pyrazolin-1-yl]-benzenesulfonylurea derivatives and their corresponding pyrazoles were synthesized. Some compounds were tested for hypoglycemic activity. Preliminary biological testing revealed that the compound showed potent antidiabetic activity.

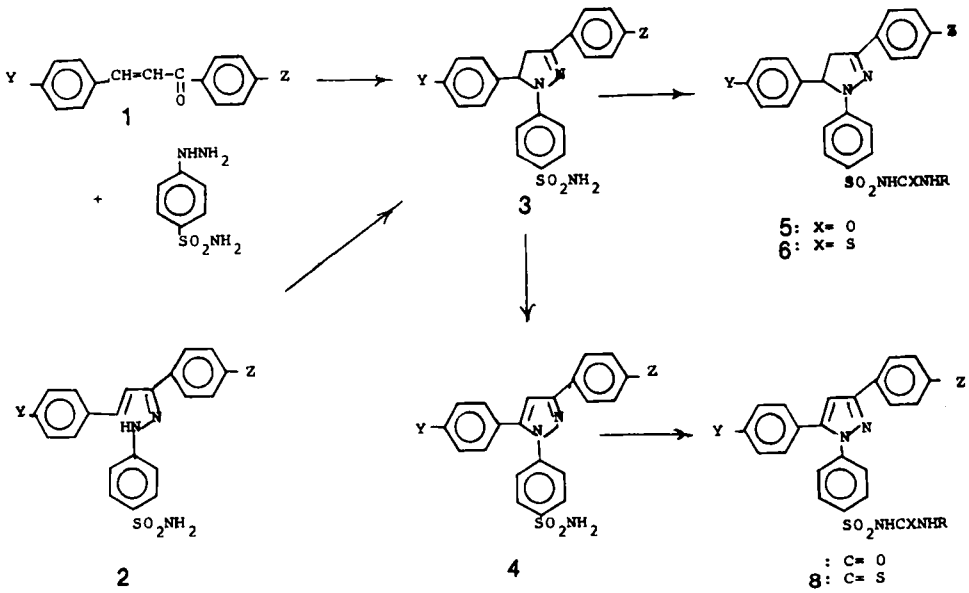
1-(*p*-Sulfamylphenyl)3,5-diaryl-2-pyrazolines (3) were prepared by condensation of the appropriate chalcone (1) with *p*-sulfamylphenylhydrazine hydrochloride. The resulting benzenesulfonamides were either treated with the appropriate isocyanate or isothiocyanate to afford the corresponding urea or thiourea derivatives, or oxidized with bromine water to the corresponding pyrazoles and similarly treated with the appropriate isocyanate or isothiocyanate to afford their corresponding urea or thiourea derivatives.

The physical and analytical data of these new pyrazolines and pyrazoles are listed in Tables I–III. The antidiabetic activity of some of these compounds is given in Table IV.

## Experimental Section

Melting points were determined in open glass capillaries and are uncorrected. The IR spectra were determined using sodium chloride plates on a Perkin Elmer 297 spectrophotometer as a solution in bromoform. The $^1H$ NMR spectra were recorded on a Varian A 60 spectrometer using $Me_4Si$ as the internal standard. The $^{13}C$ NMR spectra were recorded on a Jeol JNH-FX 100 NMR spectrometer.

**1-(*p*-Sulfamylphenyl)-hydrazones (2; Table V)**—A solution of the appropriate chalcone (1, 0.1 mol) in ethanol (100 mL) was refluxed with a mixture of *p*-sulfamylphenylhydrazine hydrochloride (0.1 mol) and sodium acetate (0.12 mol) in water (10 mL) for 1 h over a steam bath, concentrated, cooled, and poured into water. The crude hydrazones were separated and recrystallized from methanol to yield yellow needles. The IR spectra of these compounds revealed two absorption bands at 1330–1355 and 1170–1190 $cm^{-1}$ that are




Scheme



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**Table I—Substituted *p*-(3,5-Diaryl-2-pyrazolin-1-yl)-benzene sulfonylurea (5) and Thiourea (6) Derivatives**

| Compound | R | X | Y | Z | Yield, % | Melting Point | Formula | | Analysis, % Calc. | Analysis, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | $(CH_2)_2CH_3$ | O | $CH_3$ | H | 82 | 183 | $C_{26}H_{28}N_4O_3S$ | C | 65.5 | 65.6 |
| | | | | | | | | H | 5.9 | 6.0 |
| | | | | | | | | N | 11.8 | 12.0 |
| **5b** | $(CH_2)_3CH_3$ | O | $CH_3$ | H | 70 | 198 | $C_{27}H_{30}N_4O_3S$ | C | 66.1 | 66.1 |
| | | | | | | | | H | 6.1 | 6.2 |
| | | | | | | | | N | 11.4 | 11.4 |
| **5c** | $C_6H_{11}$ | O | $CH_3$ | H | 75 | 202 | $C_{29}H_{32}N_4O_3S$ | C | 67.4 | 67.5 |
| | | | | | | | | H | 6.2 | 6.0 |
| | | | | | | | | N | 10.9 | 11.0 |
| **5d** | $C_6H_5$ | O | $CH_3$ | H | 80 | 195 | $C_{29}H_{26}N_4O_3S$ | C | 68.2 | 68.1 |
| | | | | | | | | H | 5.1 | 5.2 |
| | | | | | | | | N | 11.0 | 10.9 |
| **5e** | $(CH_2)_2CH_3$ | O | Cl | H | 80 | 212 | $C_{25}H_{25}ClN_4O_3S$ | C | 60.4 | 60.5 |
| | | | | | | | | H | 5.0 | 5.2 |
| | | | | | | | | N | 11.3 | 11.1 |
| **5f** | $(CH_2)_3CH_3$ | O | Cl | H | 71 | 196 | $C_{26}H_{27}ClN_4O_3S$ | C | 62.0 | 61.8 |
| | | | | | | | | H | 5.2 | 5.3 |
| | | | | | | | | N | 10.7 | 10.9 |
| **5g** | $C_6H_{11}$ | O | Cl | H | 78 | 207 | $C_{28}H_{29}ClN_4O_3S$ | C | 64.9 | 65.0 |
| | | | | | | | | H | 5.4 | 5.5 |
| | | | | | | | | N | 10.4 | 10.3 |
| **5h** | $C_6H_5$ | O | Cl | H | 80 | 198 | $C_{28}H_{23}ClN_4O_3S$ | C | 63.3 | 63.2 |
| | | | | | | | | H | 4.3 | 4.3 |
| | | | | | | | | N | 10.6 | 10.5 |
| **5i** | $(CH_2)_2CH_3$ | O | Br | H | 83 | 197 | $C_{25}H_{25}BrN_4O_3S$ | C | 55.5 | 55.6 |
| | | | | | | | | H | 4.6 | 4.7 |
| | | | | | | | | N | 10.4 | 10.5 |
| **5j** | $(CH_2)_3CH_3$ | O | Br | H | 69 | 210 | $C_{26}H_{27}BrN_4O_3S$ | C | 56.2 | 56.0 |
| | | | | | | | | H | 4.9 | 5.0 |
| | | | | | | | | N | 10.8 | 10.7 |
| **5k** | $C_6H_{11}$ | O | Br | H | 76 | 164 | $C_{28}H_{29}BrN_4O_3S$ | C | 57.8 | 58.0 |
| | | | | | | | | H | 5.0 | 5.0 |
| | | | | | | | | N | 9.6 | 9.6 |
| **5l** | $C_6H_5$ | O | Br | H | 82 | 157 | $C_{28}H_{23}BrN_4O_3S$ | C | 58.4 | 58.5 |
| | | | | | | | | H | 4.0 | 4.0 |
| | | | | | | | | N | 9.7 | 9.8 |
| **5m** | $(CH_2)_2CH_3$ | O | H | $CH_3$ | 85 | 186 | $C_{26}H_{28}N_4O_3S$ | C | 65.5 | 65.6 |
| | | | | | | | | H | 5.9 | 6.0 |
| | | | | | | | | N | 11.8 | 12.0 |
| **5n** | $(CH_2)_3CH_3$ | O | H | $CH_3$ | 73 | 200 | $C_{27}H_{30}N_4O_3S$ | C | 66.1 | 66.3 |
| | | | | | | | | H | 6.1 | 6.3 |
| | | | | | | | | N | 11.4 | 11.2 |
| **5o** | $C_6H_{11}$ | O | H | $CH_3$ | 75 | 202 | $C_{29}H_{32}N_4O_3S$ | C | 67.4 | 67.3 |
| | | | | | | | | H | 6.2 | 6.1 |
| | | | | | | | | N | 10.9 | 11.0 |
| **5p** | $C_6H_5$ | O | H | $CH_3$ | 80 | 195 | $C_{29}H_{26}N_4O_3S$ | C | 68.2 | 68.0 |
| | | | | | | | | H | 5.1 | 5.0 |
| | | | | | | | | N | 11.0 | 10.8 |
| **6a** | $CH_2CH{=}CH_2$ | S | $CH_3$ | H | 72 | 138 | $C_{26}H_{26}N_4O_2S_2$ | C | 63.7 | 63.8 |
| | | | | | | | | H | 5.3 | 5.2 |
| | | | | | | | | N | 11.4 | 11.5 |
| **6b** | $(CH_2)_3CH_3$ | S | $CH_3$ | H | 76 | 186 | $C_{27}H_{30}N_4O_2S_2$ | C | 64.0 | 64.1 |
| | | | | | | | | H | 5.9 | 6.0 |
| | | | | | | | | N | 11.7 | 11.5 |
| **6c** | $C_6H_{11}$ | S | $CH_3$ | H | 75 | 167 | $C_{29}H_{32}N_4O_2S_2$ | C | 65.4 | 65.5 |
| | | | | | | | | H | 6.0 | 6.1 |
| | | | | | | | | N | 10.5 | 10.5 |
| **6d** | $C_6H_5$ | S | $CH_3$ | H | 80 | 159 | $C_{29}H_{26}N_4O_2S_2$ | C | 66.2 | 66.0 |
| | | | | | | | | H | 4.9 | 5.0 |
| | | | | | | | | N | 10.6 | 10.5 |
| **6e** | $C_6H_5CH_2$ | S | $CH_3$ | H | 78 | 134 | $C_{30}H_{28}N_4O_2S_2$ | C | 66.7 | 66.6 |
| | | | | | | | | H | 5.2 | 5.1 |
| | | | | | | | | N | 10.4 | 10.5 |
| **6f** | $CH_2CH{=}CH_2$ | S | Cl | H | 70 | 128 | $C_{25}H_{23}N_4O_2S_2$ | C | 58.8 | 59.0 |
| | | | | | | | | H | 4.5 | 4.5 |
| | | | | | | | | N | 11.0 | 11.1 |
| **6g** | $(CH_2)_3CH_3$ | S | Cl | H | 72 | 152 | $C_{26}H_{27}ClN_4O_2S_2$ | C | 59.3 | 59.5 |
| | | | | | | | | H | 5.1 | 5.0 |
| | | | | | | | | N | 10.6 | 10.5 |
| **6h** | $C_6H_{11}$ | S | Cl | H | 70 | 194 | $C_{28}H_{29}ClN_4O_2S_2$ | C | 60.8 | 61.0 |
| | | | | | | | | H | 5.2 | 5.3 |
| | | | | | | | | N | 10.1 | 10.0 |

**(Continued)**

**Table I—Continued**

| Compound | R | X | Y | Z | Yield, % | Melting Point | Formula | | Analysis, % Calc. | Analysis, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| **6i** | $C_6H_5$ | S | Cl | H | 78 | 181 | $C_{28}H_{23}ClN_4O_2S_2$ | C | 61.5 | 61.6 |
| | | | | | | | | H | 4.2 | 4.2 |
| | | | | | | | | N | 10.2 | 10.4 |
| **6j** | $C_6H_5CH_2$ | S | Cl | H | 75 | 157 | $C_{29}H_{25}ClN_4O_2S_2$ | C | 62.1 | 62.0 |
| | | | | | | | | H | 4.5 | 4.5 |
| | | | | | | | | N | 10.0 | 9.9 |
| **6k** | $CH_2CH{=}CH_2$ | S | Br | H | 70 | 144 | $C_{25}H_{23}BrN_4O_2S_2$ | C | 54.1 | 54.1 |
| | | | | | | | | H | 4.1 | 4.0 |
| | | | | | | | | N | 10.1 | 10.0 |
| **6l** | $(OH_2)_3CH_3$ | S | Br | H | 73 | 159 | $C_{26}H_{27}BrN_4O_2S_2$ | C | 54.6 | 54.6 |
| | | | | | | | | H | 4.7 | 4.6 |
| | | | | | | | | N | 9.8 | 10.0 |
| **6m** | $C_6H_{11}$ | S | Br | H | 70 | 190 | $C_{28}H_{29}BrN_4O_2S_2$ | C | 56.3 | 56.2 |
| | | | | | | | | H | 4.9 | 5.0 |
| | | | | | | | | N | 9.4 | 9.5 |
| **6n** | $C_6H_5$ | S | Br | H | 78 | 178 | $C_{28}H_{23}BrN_4O_2S_2$ | C | 56.9 | 57.0 |
| | | | | | | | | H | 3.9 | 3.8 |
| | | | | | | | | N | 9.5 | 9.6 |
| **6o** | $C_6H_5CH_2$ | S | Br | H | 73 | 121 | $C_{29}H_{25}BrN_4O_2S_2$ | C | 57.5 | 57.6 |
| | | | | | | | | H | 4.1 | 4.2 |
| | | | | | | | | N | 9.3 | 9.5 |
| **6p** | $CH_2CH{=}CH_2$ | S | H | $CH_3$ | 70 | 174 | $C_{26}H_{26}N_4O_2S_2$ | C | 63.7 | 63.7 |
| | | | | | | | | H | 5.3 | 5.3 |
| | | | | | | | | N | 11.4 | 11.3 |
| **6q** | $(CH_2)_3CH_3$ | S | H | $CH_3$ | 76 | 182 | $C_{27}H_{30}N_4O_2S_2$ | C | 64.0 | 63.9 |
| | | | | | | | | H | 5.9 | 6.0 |
| | | | | | | | | N | 11.7 | 11.9 |
| **6r** | $C_6H_{11}$ | S | H | $CH_3$ | 72 | 187 | $C_{29}H_{32}N_4O_2S_2$ | C | 65.4 | 65.5 |
| | | | | | | | | H | 6.0 | 5.9 |
| | | | | | | | | N | 10.5 | 10.5 |
| **6s** | $C_6H_5$ | S | H | $CH_3$ | 75 | 168 | $C_{29}H_{26}N_4O_2S_2$ | C | 66.2 | 66.3 |
| | | | | | | | | H | 4.9 | 5.1 |
| | | | | | | | | N | 10.6 | 10.7 |
| **6t** | $C_6H_5CH_2$ | S | H | $CH_3$ | 70 | 140 | $C_{30}H_{28}N_4O_2S_2$ | C | 66.7 | 66.7 |
| | | | | | | | | H | 5.2 | 5.3 |
| | | | | | | | | N | 10.4 | 10.5 |

**Table II—Substituted *p*-(3,5-Diarylpyrazol-1-yl)-benzenesulfonylurea (7) and Thiourea (8) Derivatives**

| Compound | R | X | Y | Z | Yield, % | Melting Point | Formula | | Analysis, % Calc. | Analysis, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| **7a** | $(CH_2)_2CH_3$ | O | $CH_3$ | H | 80 | 152 | $C_{26}H_{25}N_4O_3S$ | C | 66.0 | 66.2 |
| | | | | | | | | H | 5.3 | 5.4 |
| | | | | | | | | N | 11.8 | 12.0 |
| **7b** | $(CH_2)_3CH_3$ | O | $CH_3$ | H | 70 | 160 | $C_{27}H_{28}N_4O_3S$ | C | 66.4 | 66.5 |
| | | | | | | | | H | 5.7 | 5.7 |
| | | | | | | | | N | 11.5 | 11.5 |
| **7c** | $C_6H_{11}$ | O | $CH_3$ | H | 72 | 150 | $C_{29}H_{30}N_4O_3S$ | C | 67.7 | 67.7 |
| | | | | | | | | H | 5.8 | 5.9 |
| | | | | | | | | N | 10.9 | 11.0 |
| **7d** | $C_6H_5$ | O | $CH_3$ | H | 79 | 194 | $C_{29}H_{24}N_4O_3S$ | C | 68.5 | 68.4 |
| | | | | | | | | H | 4.7 | 4.6 |
| | | | | | | | | N | 11.0 | 10.9 |
| **7e** | $(CH_2)_2CH_3$ | O | Cl | H | 78 | 145 | $C_{25}H_{23}ClN_4O_3S$ | C | 60.7 | 60.8 |
| | | | | | | | | H | 4.7 | 4.7 |
| | | | | | | | | N | 11.3 | 11.5 |
| **7f** | $C_6H_5$ | O | Cl | H | 80 | 162 | $C_{28}H_{21}ClN_4O_3S$ | C | 63.4 | 63.5 |
| | | | | | | | | H | 4.0 | 4.0 |
| | | | | | | | | N | 10.6 | 10.5 |
| **7g** | $(CH_2)_2CH_3$ | O | Br | H | 70 | 150 | $C_{25}H_{23}BrN_4O_3S$ | C | 55.7 | 55.6 |
| | | | | | | | | H | 4.3 | 4.4 |
| | | | | | | | | N | 10.4 | 10.4 |
| **7h** | $C_6H_5$ | O | Br | H | 75 | 158 | $C_{28}H_{21}BrN_4O_3S$ | C | 58.7 | 58.7 |
| | | | | | | | | H | 3.7 | 3.8 |
| | | | | | | | | N | 9.8 | 9.7 |
| **7i** | $C_6H_5$ | O | H | $CH_3$ | 78 | 172 | $C_{29}H_{24}N_4O_3S$ | C | 68.5 | 68.6 |
| | | | | | | | | H | 4.7 | 4.6 |
| | | | | | | | | N | 11.0 | 11.0 |

**(Continued)**

**Table II—Continued**

| Compound | R | X | Y | Z | Yield, % | Melting Point | Formula | | Analysis, % Calc. | Analysis, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| **8a** | $C_6H_{11}$ | S | $CH_3$ | H | 79 | 174 | $C_{29}H_{30}N_4O_2S_2$ | C | 65.7 | 65.8 |
| | | | | | | | | H | 5.7 | 5.8 |
| | | | | | | | | N | 10.6 | 10.5 |
| **8b** | $C_6H_5$ | S | $CH_3$ | H | 75 | 168 | $C_{29}H_{24}N_4O_2S_2$ | C | 66.4 | 66.5 |
| | | | | | | | | H | 4.6 | 4.7 |
| | | | | | | | | N | 10.7 | 10.6 |
| **8c** | $C_6H_5CH_2$ | S | $CH_3$ | H | 80 | 155 | $C_{30}H_{26}N_4O_2S_2$ | C | 66.9 | 67.0 |
| | | | | | | | | H | 4.8 | 4.9 |
| | | | | | | | | N | 10.4 | 10.5 |
| **8d** | $CH_2CH{=}CH_2$ | S | Cl | H | 70 | 138 | $C_{25}H_{21}ClN_4O_2S_2$ | C | 59.0 | 59.1 |
| | | | | | | | | H | 4.1 | 4.1 |
| | | | | | | | | N | 11.0 | 11.1 |
| **8e** | $C_6H_{11}$ | S | Cl | H | 74 | 167 | $C_{28}H_{27}ClN_4O_2S_2$ | C | 61.0 | 61.1 |
| | | | | | | | | H | 4.9 | 5.0 |
| | | | | | | | | N | 10.2 | 10.2 |
| **8f** | $C_6H_5$ | S | Cl | H | 78 | 185 | $C_{28}H_{21}ClN_4O_2S_2$ | C | 61.7 | 61.6 |
| | | | | | | | | H | 3.9 | 4.0 |
| | | | | | | | | N | 10.3 | 10.2 |
| **8g** | $C_6H_5CH_2$ | S | Br | H | 76 | 157 | $C_{29}H_{23}BrN_4O_2S_2$ | C | 62.3 | 62.2 |
| | | | | | | | | H | 4.1 | 4.2 |
| | | | | | | | | N | 10.0 | 9.9 |
| **8h** | $CH_2CH{=}CH_2$ | S | Br | H | 70 | 138 | $C_{25}H_{21}BrN_4O_2S_2$ | C | 54.3 | 54.5 |
| | | | | | | | | H | 3.8 | 4.0 |
| | | | | | | | | N | 9.9 | 9.8 |
| **8i** | $C_6H_{11}$ | S | Br | H | 73 | 142 | $C_{28}H_{27}BrN_4O_2S_2$ | C | 58.5 | 58.4 |
| | | | | | | | | H | 4.5 | 4.6 |
| | | | | | | | | N | 9.4 | 9.5 |
| **8j** | $C_6H_5$ | S | Br | H | 75 | 158 | $C_{28}H_{21}BrN_4O_2S_2$ | C | 57.0 | 57.1 |
| | | | | | | | | H | 3.6 | 3.7 |
| | | | | | | | | N | 9.5 | 9.6 |

**Table III—Nuclear Magnetic Resonance Spectral Data of Pyrazoline and Pyrazole Derivatives[a]**

| Compound | Y | Z | $^1$H NMR: Pyrazoline H H-4 (2H,m) | $^1$H NMR: Pyrazoline H H-5 (1H,m) | $^1$H NMR: Other H | $^{13}$C NMR: Pyrazoline C C-4 | $^{13}$C NMR: Pyrazoline C C-5 | $^{13}$C NMR: Other C |
|---|---|---|---|---|---|---|---|---|
| **3** | $CH_3$ | H | 2.8–4.1 | 5.4 | 7.0–7.9(13H,m)<br>6.5(2H, s, $NH_2$)<br>2.3(3H, s, $CH_3$) | 43.1 | 62.6 | 149.0, 146.1, 138.4, 137.0, 132.7, 131.8, 129.6, 129.0, 128.4, 127.1, 125.8, 125.5, 112.0, 20.7($CH_3$) |
| **3** | Cl | H | 2.9–4.1 | 5.3 | 6.9–7.9(13H,m)<br>6.5(2H, s, $NH_2$) | 43.0 | 62.4 | 148.9, 146.0, 140.0, 133.2, 131.7, 131.3, 129.2, 128.5, 127.6, 127.0, 125.9, 120.3, 111.9 |
| **3** | Br | H | 2.9–4.3 | 5.2 | 7.0–8.0(13H, m)<br>6.7(2H, s, $NH_2$) | 42.7 | 62.0 | 148.8, 145.7, 140.4, 133.0, 131.8, 131.7, 129.0, 128.3, 127.5, 127.0, 125.7, 120.8, 111.8 |
| **3** | H | $CH_3$ | 3.0–4.2 | 5.4 | 6.9–8.0(13H, m)<br>6.7(2H, s, $NH_2$)<br>2.3(3H, s, $CH_3$) | 43.3 | 62.6 | 149.3, 146.2, 141.5, 132.3, 129.8, 129.0, 128.3, 127.5, 127.1, 125.5, 124.3, 113.9, 111.7, 20.8($CH_3$) |

**(Continued)**

**Table III—Continued**

| Compound | Y | Z | $^1$H NMR | | | $^{13}$C NMR | | |
|---|---|---|---|---|---|---|---|---|
| | | | Pyrazoline H | | Other H | Pyrazoline C | | Other C |
| | | | H-4 (2H,m) | H-5 (1H,m) | | C-4 | C-5 | |
| **4** | $CH_3$ | H | | | 7.0–8.3(14H, m)<br>6.4(2H, s, $NH_2$)<br>2.4(3H, s, $CH_3$) | | | 148.1, 144.3, 142.0, 135.2, 132.1, 131.9, 130.4, 129.2, 128.9, 128.3, 126.4, 125.4, 122.0, 120.1, 111.9, 20.9($CH_3$) |
| **4** | Cl | H | | | 7.0–8.2(14H, m)<br>6.3(2H, s, $NH_2$) | | | 148.2, 143.2, 140.8, 136.6, 135.1, 134.6, 131.6, 130.3, 129.4, 128.8, 127.9, 126.1, 122.4, 121.7, 112.0 |
| **4** | Br | H | | | 7.0–8.3(14H, m)<br>6.5(2H, s, $NH_2$) | | | 149.4, 143.5, 140.7, 136.3, 135.3, 132.0, 131.6, 131.3, 129.4, 128.6, 128.0, 126.1, 122.1, 121.2, 112.1 |
| **4** | H | $CH_3$ | | | 7.1–8.4(14H, m)<br>6.6(2H, s, $NH_2$)<br>2.4(3H, s, $CH_3$) | | | 148.0, 144.0, 142.0, 135.6, 132.0, 131.8, 130.8, 129.6, 129.3, 128.7, 126.4, 125.2, 121.6, 113.6, 111.6, 21.0($CH_3$) |

[a] Solutions in $CDCl_3$; δ in ppm; s: singlet, m: multiplet.

**Table IV—Antidiabetic Activity of Substituted *p*-(3,5-Diaryl-2-pyrazolin-1-yl)- and *p*-(2,5-Diarylpyrazol-1-yl)-benzenesulfonylurea Derivatives**

| Compound | Reduction in Plasma Glucose Level, %[a] |
|---|---|
| **5c** | 3 |
| **5e** | 3.5 |
| **5f** | 5[c] |
| **5j** | 3 |
| **5n** | 4 |
| **6a** | 3.5 |
| **6h** | 2.8 |
| **6o** | 1 |
| **7a** | 7[c] |
| **7b** | 8.3[b] |
| **7c** | 9[b] |
| **7d** | 5.5 |
| **7e** | 12[b] |
| **7f** | 6[c] |
| **7g** | 8[b] |
| **7h** | 5[c] |
| **7i** | 6.5[b] |
| **8b** | 4 |
| **8d** | 5.5[b] |
| **8h** | 3 |

[a] Tested using alloxan-treated mice (100 mg/kg); phenformin (0.4 mmol) was used as the positive control; the hypoglycemic activity of phenformin was 10% reduction (statistically significant when compared with the untreated controls, $p < 0.01$). [b] Statistically significantly different when compared with the untreated controls at $p < 0.01$. [c] Statistically significantly different when compared with the untreated controls at $p < 0.05$.

indicative of the $SO_2N<$ group, a band at 3360–3400 $cm^{-1}$ that is indicative of the NH group, and two bands at 3210–3250 and 3308–3320 $cm^{-1}$ for the $NH_2$ group.

**1-(*p*-Sulfamylphenyl)-3,5-diaryl-2-pyrazolines (3; Table VI)**—A mixture of *p*-sulfamylphenylhydrazine hydrochloride (0.1 mol) and the appropriate chalcone (0.1 mol) in ethanol (150 mL) was refluxed for 6 h over a steam bath, concentrated, and allowed to cool. The crude products that separated out were recrystallized from ethanol as needles. The IR spectra of these pyrazolines showed two absorption bands at 1330–1350 and 1170–1180 $cm^{-1}$ for the $SO_2N<$ group, and bands at 3230–3255 and 3310–3330 $cm^{-1}$ that are indicative of the $NH_2$ group.

The pyrazolines (3) were also prepared in 75–85% yield by heating their corresponding hydrazones (2) over a steam bath with a few drops of hydrochloric acid for 1 h.

**1-(*p*-Sulfamylphenyl)-3,5-diarylpyrazoles (4; Table VI)**—A suspension of the appropriate pyrazoline (0.01 mol) in water (20 mL) was treated with 5% bromine water until a faint yellow color persisted. The mixture was stirred for 2 h and the crude pyrazoles were filtered and recrystallized from methanol as needles. The IR spectra exhibited two bands at 1335–1360 and 1155–1180 $cm^{-1}$ for the $SO_2N<$ group, and bands at 3230–3250 and 3320–3340 $cm^{-1}$ for the $NH_2$ group.

**Substituted *p*-(3,5-Diaryl-2-pyrazolin-1-yl)-benzenesulfonylurea (5) and *p*-(3,5-Diarylpyrazol-1-yl)-benzenesulfonylurea[13] (7) Derivatives**—A mixture of 3 or 4 (0.05 mol) and anhydrous potassium carbonate (0.1 mol) in dry acetone (100 mL) was stirred and refluxed for 1.5 h. At this temperature, a solution of the appropriate isocyanate (0.075 mol) in dry acetone (20 mL) was added in a dropwise manner. After the mixture was stirred and refluxed overnight, acetone was removed under reduced pressure and the solid residue was dissolved in water. The crude product was isolated by acidification with 2 M hydrochloric acid and purified by recrystallization from ethanol as needles. The IR spectra of these compounds

revealed two absorption bands at 1550–1350 and 1170–1190 $cm^{-1}$ that are indicative of the $SO_2N<$ group, in addition to a urea band at 1660–1665 $cm^{-1}$.

**Substituted *p*-(3,5-Diaryl-2-pyrazolin-1-yl)-benzenesulfonylthiourea (6) and *p*-(3,5-Diarylpyrazol-1-yl)-benzenesulfonylthiourea (8) Derivatives**—A mixture of 3 or 4 (0.05 mol) and anhydrous potassium carbonate (0.1 mol) in dry acetone (100 mL) was stirred and treated with the appropriate isothiocyanate (0.06 mol). After the mixture was stirred and refluxed for 10 h, acetone was removed under reduced pressure. The solid mass thus obtained was dissolved in water and acidified with 2 M hydrochloric acid. The crude product was purified by recrystallization from ethanol as needles. The IR spectra of these compounds showed a characteristic band in the region 1100–1140 $cm^{-1}$ that is indicative of the C=S group, besides two bands at 1330–1360 and 1120–1190 $cm^{-1}$ that are indicative of the $SO_2N<$ group.

The $^1H$ NMR spectra of pyrazoline 3 exhibited, besides the aromatic protons at $\delta$ 6.9–8.0, two multiplets at $\delta$ 2.8–4.3 and 5.2–5.4 for H-4 ($CH_2$) and H-5 (CH), respectively, as well as an exchangeable $NH_2$ signal at $\delta$ 6.5–6.7. On the other hand, the $^1H$ NMR spectra of the pyrazoles (4) showed a multiplet (14 protons) at $\delta$ 7.0–8.3 for the benzene ring protons together with H-4 of the pyrazole ring, as well as the exchangeable $NH_2$ signal at $\delta$ 6.3–6.6

The $^{13}C$ NMR spectra of the pyrazoline 3 showed, besides the aromatic carbons, two signals at $\delta$ 42.7–43.3 and 62.0–62.6 for C-4 and C-5, respectively, of the pyrazoline ring.

**Biological Testing Method**—Compounds **5c, e, f, j, and n, 6a, h, and o, 7a–i,** and **8b, d, and h** were tested for hypoglycemic activity. Alloxanized female Sprague-Albino mice, 18–20 g (Alexandria University Research Center), were used. Alloxan (100 mg/kg) in a 10-mg/mL saline solution was injected into the tail vein. Three days later, the mice were given the test compounds orally in a 1%

**Table V—Hydrazone Derivatives (2)**

| Compound | Y | Z | Yield, % | Melting Point | Formula | Analysis, % | |
|---|---|---|---|---|---|---|---|
| | | | | | | Calc. | Found |
| **2a** | $CH_3$ | H | 88 | 120 | $C_{22}H_{20}N_3O_2S$ | C 67.7<br>H 5.1<br>N 10.8 | 67.9<br>5.0<br>11.0 |
| **2b** | Cl | H | 85 | 108 | $C_{21}H_{17}ClN_3O_2S$ | C 61.4<br>H 4.1<br>N 10.2 | 61.5<br>4.0<br>10.1 |
| **2c** | Br | H | 84 | 126 | $C_{21}H_{17}BrN_3O_2S$ | C 55.4<br>H 3.7<br>N 9.2 | 55.5<br>3.6<br>9.1 |
| **2d** | H | $CH_3$ | 88 | 128 | $C_{22}H_{20}N_3O_2S$ | C 67.7<br>H 5.1<br>N 10.8 | 67.8<br>5.0<br>10.9 |

**Table VI—Substituted 1-(*p*-Sulfamylphenyl)-3,5-diaryl-2-pyrazoline (3) and Pyrazole (4) Derivatives**

| Compound | Y | Z | Yield, % | Melting Point | Formula | Analysis, % | |
|---|---|---|---|---|---|---|---|
| | | | | | | Calc. | Found |
| **3a** | $CH_3$ | H | 88 | 220 | $C_{22}H_{21}N_3O_2S$ | C 67.5<br>H 5.4<br>N 10.7 | 67.6<br>5.5<br>10.8 |
| **3b** | Cl | H | 82 | 204 | $C_{21}H_{18}ClN_3O_2S$ | C 61.2<br>H 4.4<br>N 10.2 | 61.0<br>4.5<br>10.2 |
| **3c** | Br | H | 85 | 222 | $C_{21}H_{18}BrN_3O_2S$ | C 55.3<br>H 3.9<br>N 9.2 | 55.4<br>4.0<br>9.1 |
| **3d** | H | $CH_3$ | 84 | 216 | $C_{22}H_{21}N_3O_2S$ | C 67.5<br>H 5.4<br>N 10.7 | 67.5<br>5.3<br>10.5 |
| **4a** | $CH_3$ | H | 70 | 195 | $C_{22}H_{19}N_3O_2S$ | C 67.9<br>H 4.9<br>N 10.8 | 68.0<br>5.0<br>10.9 |
| **4b** | Cl | H | 68 | 152 | $C_{21}H_{16}ClN_3O_2S$ | C 61.5<br>H 3.9<br>N 10.3 | 61.6<br>4.0<br>10.2 |
| **4c** | Br | H | 72 | 186 | $C_{21}H_{16}BrN_3O_2S$ | C 55.5<br>H 3.5<br>N 9.3 | 55.6<br>3.5<br>9.4 |
| **4d** | H | $CH_3$ | 78 | 188 | $C_{22}H_{19}N_3O_2S$ | C 67.9<br>H 4.9<br>N 10.8 | 67.8<br>4.8<br>10.9 |

carboxymethylcellulose suspension at the rate of 0.4 mmol/kg. On each day of the experiment, a group of four mice was used as the control; one group of four mice was given the standard 100 mg (0.4 mmol) of phenformin/kg. Up to five groups of four mice each received the test compounds. Blood samples were collected into a 0.04% NaF solution at 0, 1, and 3 h.

Glucose was determined by the fluorescence polarization immunoassay of Abbott.[14] Results are expressed as a percent reduction of plasma glucose levels compared with the control value. Statistical significance was assessed by the *t* test, where the calculated *t* value exceeded the tabulated *t* value at the $p = 0.05$ level.

From the results cited in Table IV, it is obvious that among the four new series of substituted *p*-(3,5-diarylpyrazole)-benzenesulfonylurea derivatives only compound 7 showed marked hypoglycemic activity. The potency of most of these compounds, however, is more than that of phenformin. This study also shows that substituted pyrazole derivatives are much more active as antidiabetic agents than their corresponding 2-pyrazoline derivatives. *p*-Substitution of the aryl groups attached at the 3 or 5 positions of the pyrazole ring does not significantly influence the hypoglycemic activity of such derivatives.

From the data presented previously[8-10] and in this report, it is obvious that many 3,5-disubstituted pyrazole-benzenesulfonylurea derivatives possess marked hypoglycemic activity. Maximum activity is found in the substituted 3,5-dimethylpyrazolebenzenesulfonylurea derivatives, followed by the substituted 3-methyl-5-phenylpyrazolebenzenesulfonylurea derivatives. Substituted 3,5-diarylpyrazolebenzenesulfonylurea derivatives showed the lowest antidiabetic activity. Generally, the thiourea derivatives are much less active than the corresponding urea derivatives. Primarily, introduction of a bromine atom in the 4-position of the pyrazole ring reduces the hypoglycemic activity.

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