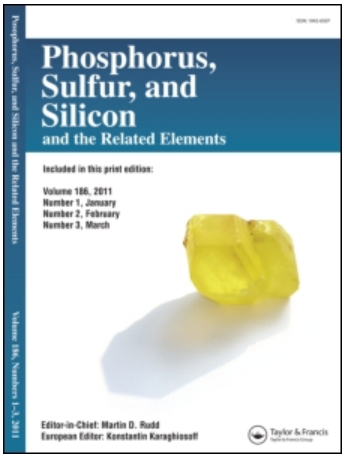

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Synthesis of 1-(2,3-Dimethyl-1-phenyl-pyrazolone-5-yl-4)-2-mercapto-1',5-cycloalkane-spiro[1,3]thiazolo[3,4-b]-1,2,4-triazole Derivatives

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SYNTHESIS OF 1-(2,3-DIMETHYL-1-PHENYL-PYRAZOLONE-5-yl-4)-2-MERCAPTO-1′,5-CYCLOALKANE-SPIRO[1,3]THIAZOLO[3,4-b]-1,2,4-TRIAZOLE DERIVATIVES

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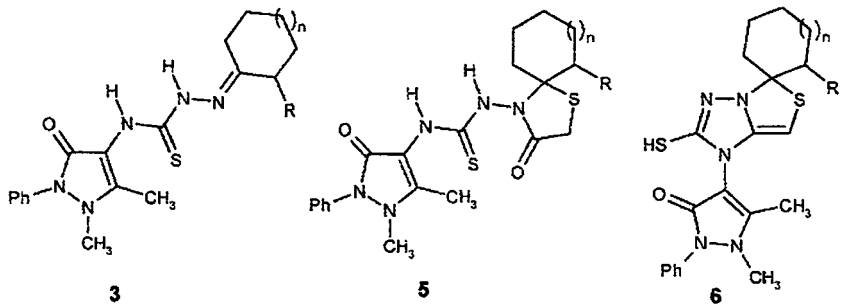
*New thiosemicarbazone derivatives **3a–c,** obtained by the condensation of 4-(2,3-dimethyl-1-phenyl-pyrazolone-5-yl-4)-thiosemicarbazide (**1**) with cycloalkanones **2a–c**, on reaction with mercaptoacetic acid (**4**) yields the corresponding spiro thiazolidin-4-ones **5a–c**. Compound **5** undergo intramolecular heterocyclization to the corresponding 1-(2,3-dimethyl-1-phenyl-pyrazolone-5-yl-4)-2-mercapto-1′,5-cycloalkane-spiro[1,3]thiazolo[3,4-b]-1,2,4-triazoles **6a–c** with NaOH.*



Keywords: Spiro thiazolidin-4-ones; synthesis; thiazolo-[3,4-b]-1,2,4-triazoles; thiosemicarbazones

Spiroheterocyclic derivatives have considerable importance as drugs and a wide scope of applications.[1–5] The pharmaceutical activities of 1,2,4-triazoles[6–9] and thiazole derivatives[10–12] have been studied extensively. Prompted by the aforesaid biological and pharmaceutical activities, and in continuation of our previous work aimed at

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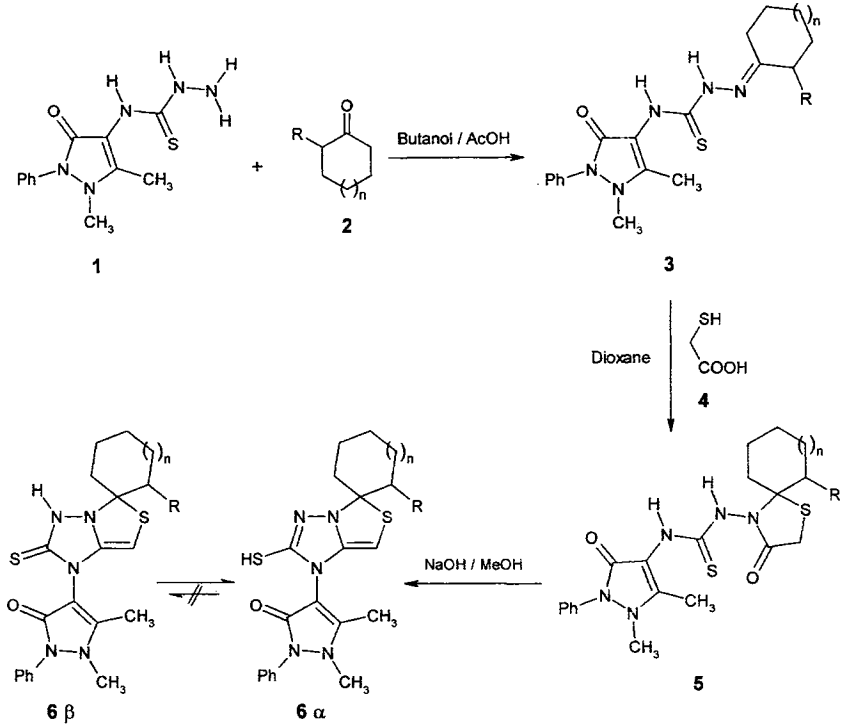
developing new approaches for the synthesis of polyfunctionally substituted heterocyclic compounds of expected biological activity,[12–17] we report here the synthesis of the versatile and hitherto unreported, otherwise difficult accessible bicyclic system 2-mercapto-1′,5-cycloalkane-spiro[1,3]thiazolo[3,4-b]-1,2,4-triazoles **6a–c** in order to study their biological activity.

RESULTS AND DISCUSSION

Thus, 1-cycloalkylidene-4-(2,3-dimethyl-1-phenylpyrazolone-5-yl-4)-thiosemicarbazones **3a–c** were synthesized by condensation of 4-(2,3-dimethyl-1-phenyl-pyrazolone-5-yl-4)-thiosemicarbazide (**1**) with cycloalkanones **2a–c** in butanol containing a catalytic amount of gl. acetic acid (Scheme 1). The structural assignments of compound **3**



2,3,5,6	n	R
a,	1	H
b,	1	CH_3
c,	2	H

SCHEME 1

was confirmed by elemental analysis as well as by IR, MS, ^{1}H NMR, and ^{13}C NMR spectra. The resonance peak of NH_2 group appearing at δ 4.72 ppm in the ^{1}H NMR of **1** disappeared in the ^{1}H NMR of **3** supporting the participation of this group in the hydrazone formation (see Experimental). The ^{13}C NMR spectrum of **3a** confirmed the proposed structural feature (Figure 1).

Addition-condensation of thiosemicarbazones **3** to mercaptoacetic acid (**4**) furnished the corresponding cycloalkane spirothiazolidin-4-ones **5a–c** (Scheme 1). The products were fully characterized through spectral and elemental analysis (see Experimental), the structure of **5** was indicated by broad IR bands around 3320 cm^{-1} corresponding to NH group, at 1685, 1650 cm^{-1}corresponding to the carbonyl group of the thiazole and pyrazole rings, and a band around 1220 cm^{-1} corresponding to C=S group. The structure elucidation for the system **5** shall be discussed here in detail for **5a**. The ^{1}H NMR spectrum in DMSO-d_6 contained a two protons singlet at δ 3.52 due to thiazolidinone protons, a two sharp singlet at δ (2.15 and 3.09) for the two methyl groups, a broad

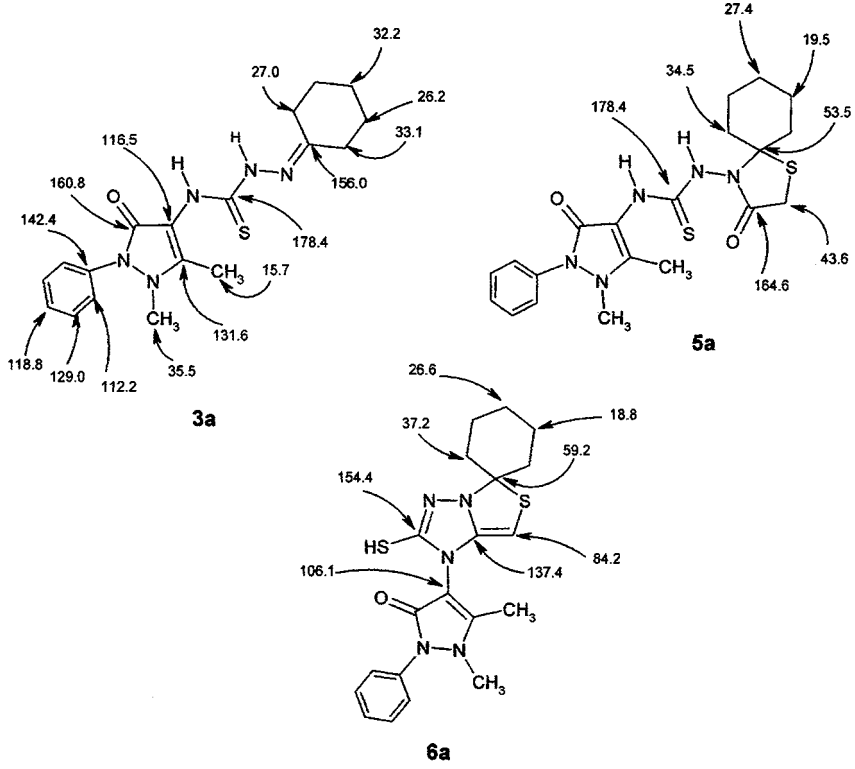


FIGURE 1 ^{13}C NMR spectral data.

singlet at δ 11.9 for the two NH groups, a ten-protons multiplet in the region of δ 1.15–2.10 due to the cyclohexyl protons and a multiplet at δ 7.2–7.4 ppm for the aromatic protons. The structure **5a** was further confirmed by ^{13}C NMR spectrum which revealed resonance at δ 53.5 and 164.6 ppm. The resonances were consistent with the quaternary sp^3 carbon (spiro carbon) and the carbonyl group of the thiazole ring respectively (Figure 1). Furthermore, the mass spectrum of **5a** gave the molecular ion peak at m/z 431 (M^+, 78%) which found to be in good agreement with the assigned structure (see Experimental).

The compound **5a** on treatment with sodium hydroxide underwent cyclization to 1-(2,3-dimethyl-1-phenyl-pyrazolone-5-yl-4)-2-mercapto-1′,5-cyclohexane-spiro[1,3]thiazolo[3,4-b]-1,2,4-triazole (**6a**) (Scheme 1). The structural assignment of **6a** was established by spectroscopic studies and elemental analysis. Thus, the mass spectrum of **6a** was compatible with the molecular formula $C_{20}H_{23}N_5OS_2$ (M^+ = 413). Its IR spectrum indicated that it exist in the iminothiol-form **6**α: There is no absorption of the N—C=S group, NH group, and C=O of thiazol ring, but band due to the SH group at 2560 cm^{-1} is observed. The tautomeric equilibrium between iminothiol-**6**α and thioamide-form **6**β seems to be widely shifted toward the iminothiol form as indicated by the ^{1}H NMR spectrum which revealed a signlet at δ 7.85 ppm assigned to the —N—(C=N—)—SH group and this peak disappear on addition of deuterium oxide. Structure **6a** was further confirmed by ^{13}C NMR spectrum which gave conclusive evidence for iminothiol-form **6**α. The spectrum reveals low-field signal at 154.4 (triazole C-2), 59.2 ppm (spiro carbon) and the other signals appeared at expected field (Figure 1). If the thioamide-form **6**β is the reaction product, one would expect a signal for the triazole C-2 to appear at higher values (see Experimental). The formation of **6a** involves intramolecular heterocyclization of **5**, thus the reaction of **5** with NaOH furnishes[18] the ambident N,S anion, the terminal nitrogen of which attacks the carbonyl carbon of 1,3-thiazole ring to yield the corresponding **6**. Compounds **6b**,**c** were prepared in similar way (Scheme 1). The structure of **6b**,**c** were confirmed on the same line as **6a** (see Experimental).

EXPERIMENTAL

All mps were recorded on a Gallen Kamp apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded (as KBr pellets) on a Shimadzu 480 spectrophotometer. The ^{1}H NMR spectra were measured in DMSO-d_6 with a Bruker AM 400 (400 MHz) spectrometer using TMS as an internal standard; the ^{13}C NMR spectra were recorded at 100 MHz.

The chemical shifts are expressed as δ values (ppm). Mass spectra were determined on a Finnigan Mat 8430 mass spectrometer operating at 70 eV. Microanalytical data were obtained from Microanalytical unit at Cairo University. Compound **1** was prepared by literature[19] and the starting materials were obtained commercially.

General Procedure for the Synthesis of 1-Cycloalkylidene-4-(2,3-dimethyl-1-phenyl-pyrazolone-5-yl-4)-thiosemicarbazones 3a–c

The thiosemicarbazide **1** (0.01 mmol) was dissolved in 20 ml of hot butanol, then cycloalkanones **2a–c** (0.01 mmol) and 1 ml of acetic acid were added and the mixture was refluxed for about 4–6 h. After cooling, the resulting product was filtered off, washed with butanol and diethyl ether, and recrystallized from AcOH/H_2O (1:1).

1-Cyclohexaylidene-4-(2,3-dimethyl-1-phenyl-pyrazolone-5-yl-4)-thiosemicarbazone (3a)

Obtained in 80% yield, m.p. 214–216°C; (found: C, 60.40; H, 6.50; N, 19.60; S, 8.90. $C_{18}H_{23}N_5OS$ requires C, 60.48; H, 6.49; N, 19.59; S, 8.97%); υ_{max}/cm^{-1} 3320–3150 (NH) 2900,2850 (—CH_2—), 1650 (CO), 1620 (C=N), 1220 (C=S); δ_H 1.41–2.10 (m, 10H, cyclohexyl protons), 2.17 (s, 3H,CH_3), 3.09 (s, 3H, N—CH_3), 7.2–7.6 (m, 5H, Ar—H), 9.3 (s, 1H, NH), 11.90 (s, 1H, NH); δ_C 15.7, 26.2, 27.0, 32.2, 33.1, 35.5, 112.2, 116.5, 118.8, 129.0, 131.6, 142.4, 156.0, 160.8, 178.4; m/z 357 (M^+, 74%).

1-(2-Methyl-cyclohexaylidene)-4-(2,3-dimethyl-1-phenylpyrazolone-5-yl-4)-thiosemicarbazone (3b)

Obtained in 78% yield, m.p. 206–208°C; (found: C, 61.50; H, 6.80; N, 18.90; S, 8.50. $C_{19}H_{25}N_5OS$ requires C, 61.43; H, 6.78; N, 18.85; S, 8.63%); υ_{max}/cm^{-1} 3300–3150 (NH), 2900,2850 (—CH_2—), 1650 (CO), 1620 (C=N), 1220 (C=S); δ_H 0.78 (d, J 6.5 Hz, 3H, CH_3), 1.43–2.11 (m, 8H, cyclohexyl protons), 2.19 (s, 3H, CH_3), 2.23 (m, 1H, CH), 3.10 (s, 3H, N—CH_3), 7.2–7.5 (m, 5H, Ar—H), 9.40 (s, 1H, NH), 11.80 (s, 1H, NH); m/z 371 (M^+, 89%).

1-Cycloheptaylidene-4-(2,3-dimethyl-1-phenyl-pyrazolone-5-yl-4)-thiosemicarbazone (3c)

Obtained in 68% yield, m.p. 208–210°C; (found: C, 61.50; H, 6.80; N, 18.80; S, 8.60. $C_{19}H_{25}N_5OS$ requires C, 61.43; H, 6.78; N, 18.85; S, 8.63%); υ_{max}/cm^{-1} 3320–3150 (NH) 2900,2850 (—CH_2—), 1650 (CO), 1620 (C=N), 1220 (C=S); δ_H 1.61–2.10 (m, 12H, cycloheptyl protons),

2.15 (s, 3H,CH_3), 3.10 (s, 3H, N—CH_3), 7.2–7.5 (m, 5H, Ar—H), 9.3 (s, 1H, NH), 11.8 (s, 1H, NH); m/z 371 (M^+, 72%).

Synthesis of Spirothiazolidinones 5a–c

To a well stirred solution of **3a–c** (0.05 mmol) in dry dioxane (50 ml) was added mercaptoacetic acid (**4**) (0.075 mmol). The reaction mixture was refluxed for 6–8 h (monitored by TLC). The clear solution thus obtained was allowed to cool, poured into ice-cold water, and neutrallized with $NaHCO_3$. The crystalline product thus formed was filtered off, washed with water, and recrystallized from dioxane.

4-[3-(2,3-Dimethyl-1-phenyl-pyrazolone-5-yl-4))-thioureido]-1-thia-4-azaspiro-[4.5]-decan-3-one (5a)

Obtained in 64% yield, m.p. 262–263°C; (found: C, 55.70; H, 5.90; N, 16.30; S, 14.80. $C_{20}H_{25}N_5O_2S_2$ requires C, 55.66; H, 5.84; N, 16.23; S, 14.86%); υ_{max}/cm^{-1} 3320–3150 (NH) 2900, 2850 (—CH_2—), 1685, 1650 (CO), 1620 (C=N), 1220 (C=S); δ_H 1.15–2.10 (m, 10H, cyclohexyl protons), 2.15 (s, 3H, CH_3), 3.09 (s, 3H, N—CH_3), 3.52 (s, 2H, thiazolidinone protons), 7.2–7.4 (m, 5H, Ar—H), 11.9 (br, s, 2 NH); δ_C 15.8, 19.5, 27.4, 34.5, 35.5, 43.6, 53.5, 112.2, 116.4, 118.8, 128.8, 131.6, 142.4, 160.8, 164.6, 178.4; m/z 431 (M^+, 78%).

4-[3-(2,3-Dimethyl-1-phenyl-pyrazolone-5-yl-4))-thioureido]-6-methyl-1-thia-4-aza-spiro[4.5]decan-3-one (5b)

Obtained in 65% yield, m.p. 242–243°C; (found: C, 56.50; H, 6.20; N, 15.80; S, 14.30. $C_{21}H_{27}N_5O_2S_2$ requires C, 56.60; H, 6.11; N, 15.72; S, 14.39%); υ_{max}/cm^{-1} 3320–3150 (NH) 2900, 2850 (—CH_2—), 1685, 1650 (CO), 1620 (C=N), 1220 (C=S); δ_H 0.80 (d, J 6.5 Hz, 3H, CH_3), 1.15–2.10 (m, 8H, cyclohexyl protons), 2.15 (s, 3H, CH_3), 2.25 (m, 1H, CH), 3.15 (s, 3H, N—CH_3), 3.46 (s, 2H, thiazolidinone protons), 7.2–7.6 (m, 5H, Ar—H), 11.8 (br, s, 2 NH); m/z 445 (M^+, 80%).

4-[3-(2,3-Dimethyl-1-phenyl-pyrazolone-5-yl-4))-thioureido]-1-thia-4-azaspiro-[4.6]-undecan-3-one (5c)

Obtained in 61% yield, m.p. 252–254°C; (found: C, 56.50; H, 6.00; N, 15.70; S, 14.40. $C_{21}H_{27}N_5O_2S_2$ requires C, 56.60; H, 6.11; N, 15.72; S, 14.39%); υ_{max}/cm^{-1} 3320–3150 (NH) 2900, 2850 (—CH_2—), 1680, 1650 (CO), 1620 (C=N), 1220 (C=S); δ_H 1.61–2.10 (m, 12H, cycloheptyl protons), 2.17 (s, 3H, CH_3), 3.10 (s, 3H, N—CH_3), 3.49 (s, 2H, thiazolidinone protons), 7.2–7.6 (m, 5H, Ar—H), 11.9 (br, s, 2 NH); m/z 445 (M^+, 82%).

Synthesis of 1-(2,3-Dimethyl-1-phenyl-pyrazolone-5-yl-4)-2-mercapto-1′,5-cycloalkane-spiro[1,3]thiazolo[3,4-b]-1,2,4-triazoles 6a–c

To a solution of NaOH (0.01 mmol) in methanol (30 ml), spirothiazolidinone **5a–c** (0.01 mmol) was added and the mixture was refluxed for 5–6 h. The solid was then collected while hot, and poured in water (50 ml), the mixture was acidified with concentrated hydrochloric acid and stirred for 1 h. The precipitated solid was filtered off, washed with water, and disolved in the minimum volume of acetone. The residue was sujected to PLC chromatography using tolune-ethylacetate (3:2) as eluent. The pure products were recrystallized from dioxane.

1-(2,3-Dimethyl-1-phenyl-pyrazolone-5-yl-4)-2-mercapto-1′,5-cyclohexane-spiro[1,3]thiazolo-[3,4-b]-1,2,4-triazole (6a)

Obtained in 64% yield, m.p. 276–278°C; (found: C, 58.20; H, 5.50; N, 17.00; S, 15.40. $C_{20}H_{23}N_5OS_2$ requires C, 58.09; H, 5.61; N, 16.93; S, 15.51%); υ_{max}/cm^{-1} 2900, 2850 (—CH_2—), 2560 (SH), 1650 (CO), 1620 (C=N); δ_H 1.12–2.10 (m, 10H, cyclohexyl protons), 2.15 (s, 3H, CH_3), 3.20 (s, 3H, N—CH_3), 7.2–7.7 (m, 6H, Ar—H and CH), 7.85 (s, 1H, SH); δ_C 15.8, 18.8, 26.6, 35.5, 37.2, 59.2, 84.2, 106.1, 112.2, 118.8, 129.0, 131.8, 137.4, 142,4, 154.4, 160.8; m/z 413 (M^+, 72%).

1-(2,3-Dimethyl-1-phenyl-pyrazolone-5-yl-4)-2-mercapto-1′,5-(2′-methyl-cyclohexane)-spiro[1,3]thiazolo[3,4-b]-1,2,4-triazole (6b)

Obtained in 60% yield, m.p. 266–268°C; (found: C, 59.00; H, 5.80; N, 16.50; S, 14.90. $C_{21}H_{25}N_5OS_2$ requires C, 58.99; H, 5.89; N, 16.38; S, 15.00%); υ_{max}/cm^{-1} 2900, 2850 (—CH_2—), 2565 (SH), 1650 (CO), 1620 (C=N); δ_H 0.79 (d, J 6.5 Hz, 3H, CH_3), 1.23–2.13 (m, 8H, cyclohexyl protons), 2.15 (s, 3H, CH_3), 2.29 (m, 1H, CH), 3.15 (s, 3H, N—CH_3), 7.2–7.7 (m, 6H, Ar—H and CH), 7.85 (s, 1H, SH); m/z 427 (M^+, 76%).

1-(2,3-Dimethyl-1-phenyl-pyrazolone-5-yl-4)-2-mercapto-1′,5-cycloheptane-spiro[1,3]-thiazolo-[3,4-b]-1,2,4-triazole (6c)

Obtained in 60% yield, m.p. 270–272°C; (found: C, 58.90; H, 6.00; N, 16.40; S, 15.00. $C_{21}H_{25}N_5OS_2$ requires C, 58.99; H, 5.89; N, 16.38; S, 15.00%); υ_{max}/cm^{-1} 2900, 2850 (—CH_2—), 2560 (SH), 1650 (CO), 1620 (C=N); δ_H 1.61–2.20 (m, 12H, cycloheptyl protons), 2.15 (s, 3H, CH_3), 3.20 (s, 3H, N—CH_3), 7.2–7.7 (m, 6H, Ar—H and CH), 7.85 (s, 1H, SH); m/z 427 (M^+, 82%).

REFERENCES

[1] J. L. Bullington and J. H. Dood, *J. Heterocycl. Chem.*, **35,** 397 (1998).
[2] T. Nagasaka, H. Sato, and S. I. Saeki, *Tetrahedron Asymmetry*, **8,** 191 (1997).
[3] M. T. Crimmins, D. G. Washburn, J. D. Katz, and F. J. Zawacki, *Tetrahedron Lett.*, **39,** 3439 (1998).
[4] H. Pellissier, P. Y. Michellys, and M. Santelli, *J. Org. Chem.*, **62,** 5588 (1995).
[5] J. A. Wendt, P. J. Gauvreau, and R. D. Bach, *J. Am. Chem. Soc.*, **116,** 992 (1994).
[6] H. Eto, Y. Kaneko, and T. Sakamotoa, *Pharm. Bull.*, **48**(7), 982 (2000).
[7] M. C. Hosur, M. B. Talawar, U. V. Laddi, R. S. Bennur, and S. C. Bennur, *Indian J. Chem.*, **34B**, 707 (1995).
[8] L. Czollner, G. Szilagyi, J. Lango, and J. Janaky, *Arch. Pharm. (Weinheim, Ger.)* **323,** 225 (1990).
[9] R. M. Jacobson and L. T. Nguyen, Eur. Pat. Appl. Ep. 338 685 (1990); *C.A.* **112,** 178991t (1990).
[10] M. V. Diurno, O. Mazzoni, E. Piscopo, and A. Bolognese, *Farmaco.* **48,** 435 (1993).
[11] R. G. Mehta, J. Liu, A. Constantinou, M. Hawthorne, J. M. Pezzuto, R. C. Moon, and R. M. Moriarty, *Anticancer Res.*, **14,** 1209 (1994).
[12] R. M. Shaker, *Phosphorus, Sulfur, and Silicon* **149,** 7 (1999).
[13] R. M. Shaker, *Die pharmazie* 148 (1996).
[14] R. M. Shaker and F. F. Abdel-Latif, *J. Chem. Res.(S)* 294 (1997).
[15] R. A. Mekheimer and R. M. Shaker, *J. Chem. Res. (S)* 76 (1999); *(M)*, 0449 (1999).
[16] R. M. Shaker, *Phosphorus, Sulfur, and Silicon* **158,** 9 (2000).
[17] R. M. Shaker, A. F. Mahmoud, and F. F. Abdel-Latif, *Phosphorus, Sulfur, and Silicon* **160,** 207 (2000).
[18] I. Ya. Postovskii, and N. N. Vereshchagina, *Zhur. Obschchei Khim.* **26,** 2583 (1956); *C.A.* **51,** 5055b (1956).
[19] M. Morita, *Yakugaku Zasshi*. **82,** 36 (1962); *C.A.* **57,** 16586d (1962).