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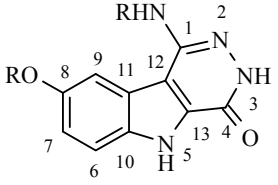
BISINDOLES. 41*. A STRAIGHTFORWARD APPROACH TOWARDS THE SYNTHESIS OF NEW BIS-PYRIDAZINOINDOLES

A. Z. Kalatozishvili[1], N. Sh. Samsonia[1], N. L. Targamadze[1], I. Sh. Chikvaidze[1], Sh. A. Samsoniya[1], A. O. Wesquet[2], and Uli Kazmaier[2]**

A set of new bis-pyridazinoindoles was obtained via cyclization of suitable bishydrazones. Key intermediates in this approach were indolecarbaldehydes and -dialdehydes.

Keywords: bisindoles, bis-pyridazinoindoles, hydrazones, indoles, bis-tricyclic systems..

Many pyridazino[4,5-*b*]indoles show high biological activity and therefore are of interest from a pharmaceutical point of view [2–5]. For example, functionaly substituted derivatives **1** were found to inhibit platelet aggregation [6, 7], while others were identified as effective intercalators of DNA [8].



1

Therefore, we were very interested in the synthesis of the corresponding symmetrical bis-tricyclic systems. Two tricycles can be bound either through the benzene ring or through the pyridazine subunit. Based on our previous work in this area, we started the synthesis (Schemes 1 and 2) with the indolecarbaldehydes **2**, **3,** and **10** [9, 10]. For this purpose, the bis-indolecarbaldehydes **2** and **3** reacted with monosubstituted hydrazines (Scheme 1), while with the aldehyde **10** the dimerization was achieved by using bishydrazines **11** (Scheme 2). In general, the bis-oxopyridazinoindoles can be obtained either from the isolated bishydrazones or directly in one pot from the aldehyde. Interestingly, the unsubstituted hydrazone derivatives **4a** and **5** could not be obtained in pure form, and therefore in this case the one-pot protocol definitely was the better choice.

* For Communication 40, see [1].

** To whom correspondence should be addressed, e-mail: shotasamsonia@yahoo.de.

[1]Iv. Javakhishvili Tbilisi State University, Tbilisi 0128, Georgia.
[2]Institut für Organische Chemie, Universität des Saarlandes, Postfach 151150, 66041 Saarbrücken, Germany; e-mail: u.kazmaier@mx.uni-saarland.de.

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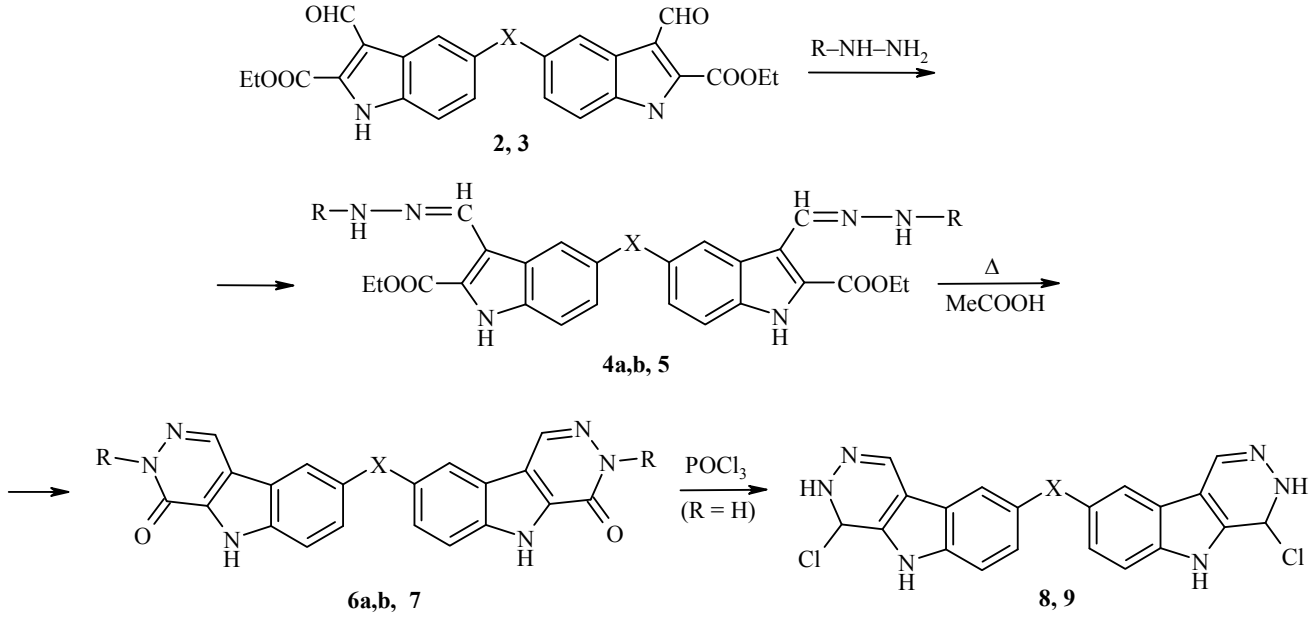
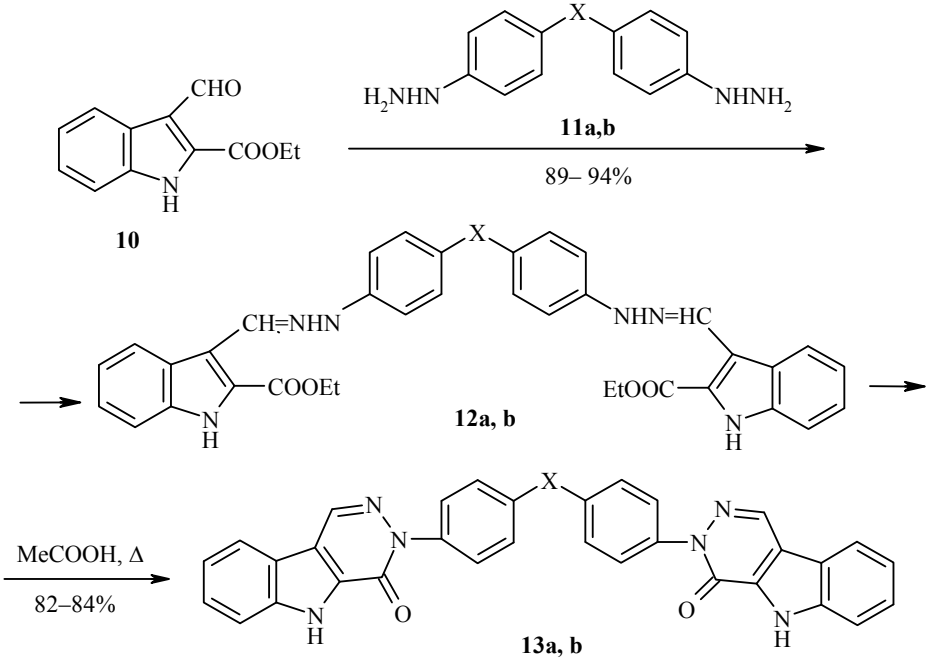
The bishydrazones **4a** and **5** were directly converted into the corresponding bis-oxopyridazinoindole. While in the two-step synthesis the bishydrazones were obtained at room temperature, in the *one-pot* approach the aldehydes were refluxed with the hydrazines in glacial acetic acid. In addition, the pyridazinones **6a** and **7** were converted into the corresponding chloro-substituted derivatives **8** and **9** using boiling $POCl_3$.

Scheme 1



4,6 a R = H, **b** R = Ph; **5,7** R = H; **2,4a,b,6a,b,8** X = O; **3,5,7,9** X = CH_2

Scheme 2



11–13 a X = O, **b** X = CH_2

EXPERIMENTAL

The course of the reaction and the purity of the compounds were monitored by TLC (Silufol UV-254). Visualization was accomplished with UV light, I_2/ethanol and a solution of Ehrlich reagent (4-dimethylaminobenzaldehyde). Preparative chromatography was conducted on silica gel with particle size 100-250 μm. The IR spectra were recorded on a Thermo Nikolet FTIR photometer AVATAR 370. The UV spectra were obtained on an UV/Vis Varian Cary 100 instrument in ethanol. ^{1}H and ^{13}C NMR spectra were recorded at the Department of Organic Chemistry, Saarland University, on a Bruker DRX-500 spectrometer (500 and 125 MHz respectively) using DMSO-d_6 as solvent. The residual proton signals of DMSO were used as the reference. IR and UV spectroscopy and elemental analysis were performed at the Department of Chemistry, Iv. Javakhishvili Tbilisi State University.

Bis[2-ethoxycarbonyl-3-(phenylhydrazonomethyl)-1H-indol-5-yl] Ether (4b). To a solution of compound **2** (1.12 g, 2.5 mmol) in DMF (60 ml), acetic acid (0.6 ml) and phenylhydrazine (1.08 g, 10 mmol) were added. The solution was stirred for 1 h at room temperature before it was poured into water (150 ml). The precipitated crystals were filtered off, washed with water, and dried. Yield 1.38 g (88%); mp 185-186ºC. R_f 0.45 (benzene–acetone, 6:1). IR spectrum (nujol), ν, cm^{-1}: 3160 (NH), 1720 (CO), 1640 (C=N). UV spectrum, λ_{max}, nm (log ε): 206 (4.46), 235 (4.29), 303 (4.21), 340 (4.19), 400 (3.97). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.93 (2H, s, H-1); 10.26 (2H, s, CH=N–N<u>H</u>); 8.67 (2H, s, C<u>H</u>=N–NH); 8.03 (2H, d, $J_{4,6}$ = 1.6, H-4); 7.27 (2H, dd, $J_{6,7}$ = 8.8, $J_{4,6}$ = 1.6, H-6); 7.55 (2H, d, $J_{6,7}$ = 8.8, H-7); 6.54–6.85 (10H, m, C_6H_5); 4.40 (4H, q, *J* = 6.9, O–C<u>H</u>$_2$–CH$_3$); 1.40 (6H, t, *J* = 7.1, CH$_2$–C<u>H</u>$_3$). Found, %: C 69.11; H 5.42; N 13.32. $C_{36}H_{32}N_6O_5$. Calculated, %: C 68.78; H 5.13; N 13.37.

Bis(3,4-dihydro-4-oxopyridazino[4,5-*b*]-5H-indol-8-yl) Ether (6a). Hydrazine hydrate (0.2 g, 4 mmol) was added to a suspension of compound **2** (0.45 g, 1 mmol) [8, 9] in acetic acid (40 ml) and the mixture was stirred at room temperature for 30 min. The obtained yellow suspension was refluxed for 1.5 h and filtered; the residue on the filter was washed with hot acetic acid and water and then dried. Yield 0.31 g (81%). After recrystallization from DMF mp > 400°C (decomp.). IR spectrum (nujol), ν, cm^{-1}: 3140 (NH ind.), 3180 (NH lact.), 1670 (CO), 1640 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.77 (2H, s, H-5); 12.67 (2H, s, H-3); 8.69 (2H, s, H-1); 7.81 (2H, s, H-9); 7.62 (2H, d, $J_{6,7}$ = 8.8, H-7); 7.29 (2H, d, $J_{6,7}$ = 8.8, H-6). ^{13}C NMR spectrum, δ, ppm: 155.6, 152.6, 135.4, 133.5, 132.4, 121.5, 119.8, 117.4, 114.3, 109.98. Found, %: C 62.23; H 3.42; N 21.90. $C_{20}H_{12}N_6O_3$. Calculated, %: C 62.50; H 3.15; N 21.87.

Bis(3,4-dihydro-4-oxopyridazino[4,5-*b*]-5H-indol-8-yl)methane (7) was obtained from compound **3** (446 mg, 1 mmol) similarly to compound **6a**. Yield 0.3 g (79%). After recrystallization from DMF mp > 364°C (decomp.). IR spectrum (nujol), ν, cm^{-1}: 3140–3180 (NH), 1680 (CO), 1630 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.77 (2H, s, H-5); 12.63 (2H, s, H-3); 8.69 (2H, s, H-1); 8.05 (2H, s, H-9); 7.53 (2H, d, $J_{6,7}$ = 8.5, H-7); 7.40 (2H, d, $J_{6,7}$ = 8.51, H-6); 4.25 (2H, s, CH$_2$). ^{13}C NMR spectrum, δ, ppm: 156.7, 137.6, 134.9, 133.3, 131.8, 128.4, 121.0, 120.8, 117.3, 113.0, 104.2. Found, %: C 65.64; H 3.87; N 21.93. $C_{21}H_{14}N_6O_2$. Calculated, %: C 65.96; H 3.69; N 21.98.

3,3'-Diphenyl-bis(3,4-dihydro-4-oxopyridazino[4,5-*b*]-5H-indol-8-yl) Ether (6b). A. A suspension of dihydrazone **4b** (628 mg, 1 mmol) in acetic acid (50 ml) was refluxed with stirring for 1.5 h. The hot suspension was filtered, and the precipitate was washed with acetic acid and water and then dried. Yield 450 mg (84%).

B. Compound **6b** was obtained from compound **2** (448 mg, 1 mmol) and phenylhydrazine (432 mg, 4 mmol) similarly to compound **6a**. Yield 440 mg (82%). After recrystallization from DMF mp 386–387°C. IR spectrum (nujol), ν, cm^{-1}: 3350 (NH), 1670 (CO), 1600 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.96 (2H, s, H-5); 8.88 (2H, s, H-1); 7.89 (2H, d, $J_{7,9}$ = 2.2, H-9); 7.68 (2H, dd, $J_{6,7}$ = 7.5, $J_{7,9}$ = 7.2, H-7); 7.36 (2H, d, $J_{6,7}$ = 7.5, H-6); 7.42–7.62 (10H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 190.3, 154.4, 152.7, 141.9, 135.9, 134.0, 132.6, 128.5, 127.8, 126.2, 121.6, 120.1, 116.8, 114.5, 110.0. Found, %: C 71.25; H 4.01; N 15.69. $C_{32}H_{20}N_6O_3$. Calculated, %: C 71.63; H 3.76; N 15.66.

Bis(3,4-dihydro-4-chloropyridazino[4,5-*b*]-5H-indol-8-yl) Ether (8). $POCl_3$ (7.5 ml, 82.2 mmol) was added dropwise at 0°C to compound **6** (384 mg, 1 mmol), and the reaction mixture was then refluxed for 5 h. The excess of $POCl_3$ was evaporated *in vacuo*, and Et_2O (50 ml) and water (50 ml) were added to the residue. The aqueous layer was then neutralized with aqueous NH_4OH. The precipitate was filtered off, washed with water, hot DMF, ethanol, and Et_2O, and then dried. Yield 350 mg (83%); mp > 341°C (decomp.). IR spectrum (KBr), ν, cm^{-1}: 3280 (NH), 1651 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.77 (2H, s, H-5); 8.69 (2H, s, H-1); 7.82 (2H, d, $J_{7,9}$ = 1.9, H-9); 7.63 (2H, dd, $J_{6,7}$ = 8.8, $J_{7,9}$ = 1.9, H-7); 7.30 (2H, d, $J_{6,7}$ = 8.8, H-6). ^{13}C NMR spectrum, δ, ppm: 190.3, 155.2, 152.6, 135.4, 133.5, 132.4, 121.6, 119.9, 114.3, 110.0. Found, %: C 57.24; H 2.60; Cl 16.42; N 20.39. $C_{20}H_{10}Cl_2N_6O$. Calculated, %: C 57.03; H 2.39; Cl 16.83; N 19.95.

Bis(3,4-dihydro-4-chloropyridazino[4,5-*b*]-5H-indol-8-yl)methane (9) was obtained similarly to compound **8** from compound **7** (382 mg, 1 mmol). Yield 330 mg (79%); mp > 330°C (decomp.). IR spectrum (KBr), ν, cm^{-1}: 3193 (NH), 1666 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.78 (2H, s, H-5); 8.69 (2H, s, H-1); 8.04 (2H, s, H-9); 7.53 (2H, d, $J_{6,7}$ = 8.5, H-7); 7.33 (2H, d, $J_{6,7}$ = 8.5, H-6); 4.24 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 155.9, 137.8, 135.2, 133.5, 132.0, 128.7, 121.2, 121.0, 117.6, 113.2, 41.6. Found, %: C 60.62; H 3.28; Cl 16.40; N 19.54. $C_{21}H_{12}Cl_2N_6$. Calculated, %: C 60.16; H 2.88; Cl 16.91; N 20.04.

2-Ethoxycarbonyl-3-formylindole 4,4'-Diphenylene Oxide Dihydrazone (12a) was obtained similarly to compound **4b** from compounds **10** (434 mg, 2 mmol) and **11a** (303 mg, 1 mmol). Yield 0.56 g (89%); mp 154-156°C. R_f 0.57 (benzene–acetone, 6:1). IR spectrum (KBr), ν, cm^{-1}: 3147-3210 (NH), 1724 (CO), 1643 (C=N). UV spectrum, λ_{max}, nm (log ε): 206 (4.54), 220 (4.45), 232 (4.31), 296 (4.19). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.72 (2H, s, H-1); 10.60 (2H, s, CH=NNH); 8.52 (2H, s, CH=NNH); 8.38 (2H, d, $J_{4,5}$ = 8.2, H-4); 7.63 (2H, d, $J_{6,7}$ = 8.2, H-7); 7.41 (2H, t, *J* = 8.2, H-6); 7.36 (2H, t, *J* = 8.2, H-5); 6.82–7.31 (8H, m, H C_6H_4); 4.50 (4H, q, *J* = 7.7, OCH_2CH_3); 1.48 (6H, t, *J* = 7.7, OCH_2CH_3). ^{13}C NMR spectrum, δ, ppm: 187.6, 176.7, 164.5, 161.4, 154.9, 149.3, 136.3, 133.5, 130.0, 124.2, 122.4, 119.9, 119.4, 118.6, 116.8, 106.1, 61.8, 14.3. Found, %: C 68.41; H 5.35; N 13.61. $C_{36}H_{32}N_6O_5$. Calculated, %: C 68.78; H 5.13; N 13.37.

2-Ethoxycarbonyl-3-formylindole 4,4'-Diphenylenemethane Dihydrazone (12b) was obtained similarly to compound **4b** from compounds **10** (434 mg, 2 mmol) and **11b** (301 mg, 1 mmol). Yield 0.59 g (94%); mp 177-179°C. R_f 0.47 (benzene–Et_2O, 2:1). IR spectrum (nujol), ν, cm^{-1}: 3327 (NH), 1722, 1680 (CO), 1614 (C=N). UV spectrum, λ_{max}, nm (log ε): 205 (4.56), 220 (4.45), 237 (4.30), 246 (4.30), 312 (4.14). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.49 (2H, s, H-1); 9.51 (2H, s, CH=NNH); 8.84 (2H, s, CH=NNH); 8.65 (2H, dd, $J_{4,5}$ = 7.8, $J_{4,6}$ = 1.2, H-4); 7.36 (2H, dd, $J_{6,7}$ = 7.8, $J_{5,7}$ = 1.2, H-7); 7.23 (2H, td, $J_{5,6}$ = $J_{6,7}$ = 7.8, $J_{4,6}$ = 1.2, H-6); 7.15 (2H, td, $J_{4,5}$ = $J_{5,6}$ = 7.8, $J_{5,7}$ = 1.2, H-5); 7.52–7.18 (8H, m, AA_1BB_1–system, H C_6H_4); 4.43 (4H, q, *J* = 7.2, OCH_2CH_3); 3.87 (2H, s, CH_2); 1.43 (6H, t, *J* = 7.2, OCH_2CH_3). ^{13}C NMR spectrum, δ, ppm: 173.6, 161.2, 160.0, 143.6, 136.7, 133.4, 131.3, 129.4, 125.5, 124.4, 124.2, 123.8, 121.1, 118.2, 113.3, 111.8, 110.2, 60.6, 14.3. Found, %: C 70.63; H 5.12; N 13.12. $C_{37}H_{34}N_6O_4$. Calculated, %: C 70.91; H 5.47; N 13.41.

4,4'-Bis(3,4-dihydro-4-oxopyridazino[4,5-*b*]-5H-indol-3-yl)diphenyl Oxide (13a). A suspension of dihydrazone **12a** (628 mg, 1 mmol) in acetic acid (50 ml) was refluxed for 1.5 h. The hot suspension was filtered and the precipitate washed with hot acetic acid and water and then dried. Yield 0.44 g (82%). Recrystallization from DMF; mp > 340°C (decomp.). IR spectrum (nujol), ν, cm^{-1}: 3147 (NH), 1651 (CO), 1605 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.99 (2H, s, H-5); 8.94 (2H, s, H-1); 8.22 (2H, d, $J_{8,9}$ = 7.5, H-9); 7.65 (2H, t, *J* = 7.5, H-7); 7.54 (2H, d, *J* = 7.5, H-6); 7.38 (2H, t, *J* = 7.5, H-8); 7.71-7.24 (8H, m, AA_1BB_1–system, H C_6H_4). ^{13}C NMR spectrum, δ, ppm: 155.5, 154.5, 139.4, 137.6, 133.8, 131.7, 130.3, 128.0, 127.3, 121.6, 121.5, 120.8, 118.9, 118.6, 116.9, 113.1. Found, %: C 71.35; H 3.92; N 15.93. $C_{32}H_{20}N_6O_3$. Calculated, %: C 71.63; H 3.76; N 15.66.

4,4'-Bis(3,4-dihydro-4-oxopyridazino[4,5-*b*]-5H-indol-3-yl)diphenylmethane (13b) was obtained similarly to compound **13a** from compounds **12b** (626 mg, 1 mmol) and **11b** (301 mg, 1 mmol). Yield 0.45 g (84%). Recrystallization from DMF; mp > 375ºC (decomp.). IR spectrum (KBr), ν, cm^{-1}: 3155 (NH), 1643 (CO); 1600 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.96 (2H, s, H-5); 8.95 (2H, s, H-1); 8.20 (2H, d,

$J_{8,9}$ = 8.2, H-9); 7.65 (2H, d, $J_{6,7}$ = 8.2, H-6); 7.40 (2H, t, J = 8.2, H-7); 7.38 (2H, t, J = 8.2, H-8); 7.61-7.28 (8H, m, AA_1BB_1–system, H C_6H_4); 4.12 (2H, s, CH_2). ^{13}C NMR spectrum, δ, ppm: 162.3, 155.6, 144.4, 143.9, 140.4, 139.6, 133.7, 129.7, 128.7, 126.3, 121.5, 120.8, 119.2, 116.8, 113.5, 110.2, 106.6. Found, %: C 74.40; H 4.37; N 15.44. $C_{33}H_{22}N_6O_2$. Calculated, %: C 74.14; H 4.15; N 15.72.

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REFERENCES

1. Sh. A. Samsoniya and M. V. Trapaidze, *Proc. Georgia Acad. Sci.*, *Chem. Ser*., **34**, 145 (2008).
2. K. Matsumoto, T**.** Uchida, K. Aoyama, M. Nishikawa, T. Kuroda, and T. Okamoto, *J. Heterocycl. Chem.*, **25**, 1793 (1988).
3. A. Monge, M. Font, P. Parrado, and E. Fernandez-Alvarez, *Anal. Quim.*, *Ser. C: Quim. Org. Bioquim.*, **8**, 270 (1988).
4. A. A. El-Gendy and H. A. El-Banna, *Arch. Pharm. Res.*, **21**, 21 (2001).
5. F. Palluotto, F. Campagna, A. Carotti, M. Ferappi, A. Rosato, and C. Vitali, *Farmaco*, **57**, 63 (2002).
6. A. Monge, P. Parrado, M. Font, and E. Fernandez-Alvarez, *J. Med. Chem.*, **30**, 1029 (1987).
7. A. Monge, M. Font, P. Parrado, and E. Fernandez-Alvarez, *Eur. J. Med. Chem. Chim. Ther.*, **23**, 547 (1988).
8. A. Molina, J. J. Vaquero, J. G. Garcia-Navio, I. Alvarez-Builla, B. de Pascual-Teresa, F. Gago, and M. M. Rodrigo, *J. Org. Chem*., **64**, 3907 (1999).
9. Sh. A. Samsoniya, I. Sh. Chikvaidze, and N. N. Suvorov, *Bull. Georg. Acad. Sci.*, **99**, 613 (1980).
10. Sh. A. Samsoniya, D. M. Tabidze, D. A. Kereselidze, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.,* 55 (1983). [*Chem. Heterocycl. Comp*., **19**, 49 (1983)].