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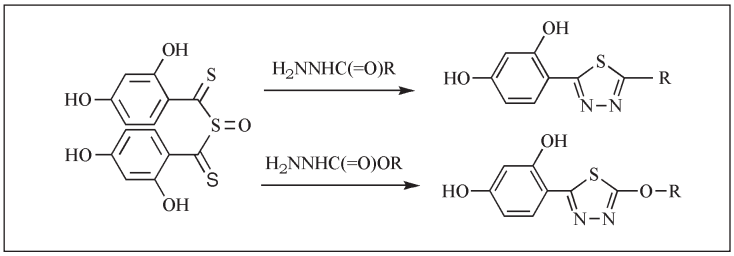

One-stage synthesis of 5-substituted (alkyl, aryl, heteroaryl, arylalkyl, heteroalkyl, alkoxy-, aryloxy)-2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles is described. The compounds were prepared by the reaction of sulfinyl-bis(2,4-dihydroxythiobenzoyl) (STB) with hydrazides or carbazates. The structure of new compounds was assigned by ir, nmr and ms data.

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Many compounds with the N-C-S linkage, in the linear and cyclic systems like thioamides, thiazoles, thiadiazoles, thiazines and corresponding fused heterocycles exhibit a large number of biological activity. Especially interesting in this respect are 1,3,4-thiadiazoles, with the double moiety mentioned above for which, depending on the type of substitutions, a very wide spectrum of biological activity is described: antitumor, antifungal, antibacterial, antituberculosis, anesthetic, antiinflammatory, anticonvulsant, cardiotonic, antihypertensive and others [1-5].

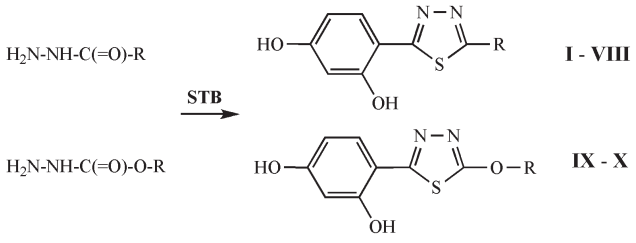
The cyclization of suitable open-chain organic molecules is a classical and common approach to the synthesis of various heterocyclic derivatives. 1,3,4-Thidiazole nucleus is usually formed by the condensation process of acylthiosemicarbazides obtained in the reaction of thiosemicarbazides with different acylating reagents using standard methods (sulfuric acid, phosphorus oxychloride, benzoyl chloride, acetyl chloride as dehydrating agents) [3-8] or microwave irradiation [9-10]. In this way 2-aminoderivatives are obtained. Oxidative cyclization of thiosemicarbazones by iron(III) chloride depending on the type of N-substitution gives thiadiazoles or thiadiazolines [11-13]. The cyclization process is favoured by electron-withdrawing groups linked to the –CH=N-N< hydrazone moiety [12-13]. Solid phase synthesis based on this reaction was described [14].

To obtain 1,3,4-thiadiazole ring thiohydrazides were also used. The linear structure of oxamic acid thiohydrazides was cyclized by haloacetyl chlorides or alkoxycarbonyl derivatives [15]. Some thiadiazoles were obtained from carboxamidrazones or hydrazonyl chloride (bromide) applying sulfur containing reagents for cyclization, carbon disulfide or potassium thiocyanate respectively [16,17,18].

Since there is little information in literature regarding the methods of synthesis of hydroxyl derivatives, and the starting materials for compounds of this type, it was of interest to develop novel, efficient routes for their preparation thus increasing the range and establishing methods for their practical usage. The electrophilic reagent sulfinyl-bis(2,4-dihydroxythiobenzoyl) (**STB**) prepared by our laboratory in the reaction with N3-substituted amidrazones gave the linear product, N1-thioacyl derivative, and cyclic, 2,5-disubstituted 1,3,4-thiadiazole [19-20]. These studies revealed that **STB** can also act as an endogeneous cyclizing reagent. Keeping in view the above facts and high activity of different groups of compounds with 2,4-dihydroxyphenyl moiety obtained by our laboratory [21-23], we report herein the preparation of a new series of compounds including both 1,3,4-thiadiazole and 2,4-dihydroxyphenyl moiety, differently 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles, with the objective of obtaining new biologically active compounds.

The novel 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles have been synthesised by the reaction of sulfinyl-bis(2,4-dihydroxythiobenzoyl) (**STB**) with commercially available hydrazides or carbazates. The synthetic pathway for the compounds under consideration is illustrated in Scheme 1. **STB** as the starting reagent was obtained from 2,4-dihydrox-

Scheme 1

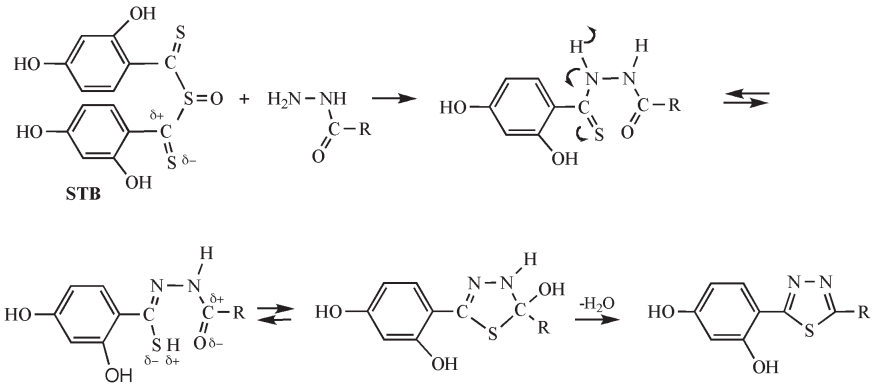


I. C_6H_5- **V.** 1-naphthyl- **IX.** C_2H_5-
II. 4-CH_3-C_6H_4- **VI.** C_6H_5-CH_2- **X.** 4-CH_3O-C_6H_4-CH_2-
III. 3-HO-C_6H_4- **VII.** 4-F-C_6H_4-OCH_2-
IV. 4-HO-C_6H_4- **VIII.** 4-pyridyl-

ybenzenecarbodithioic acid, which was prepared from resorcinol and CS_2 according to the modified Kolbe-Schmidt reaction [24]. The process of 2,4-dihydroxybenzenecarbodithioic acid with $SOCl_2$ in diethyl ether gives **STB** [19].

that is not described in literature and seems to be crucial in biological effects. Preliminary studies confirmed this finding. Some derivatives inhibit *in vitro* human tumor cell lines growth (SW707 – rectal adenocarcinoma, HCV29T –

Scheme 2



The reaction of **STB** with nucleophiles (hydrazides or carbazates) first gives the linear product of thioacyl derivative, which transforms into the thiol form [25]. In the next step cycloaddition to the partially saturated five-membered ring takes place. Elimination of water molecule finally gives the 1,3,4-thiadiazole ring (Scheme 2). The cyclization process is conditioned by proper acidity of -C(=S)NH- moiety proton and induced by –OH groups size of potential on the sulfur atom. The proposed mechanism is similar to that described by Golovlyova *et al*. for acylthiosemicarbazides [7].

In most cases the target compounds do not need extensive purification and were prepared as quite pure after the first recrystallization from methanol or methanol-water solutions. Their purity was monitored by reversed-phase (RP-18) HPLC chromatography (methanol-water). The structure of the synthesised compounds has been determined on the basis of the elemental analyses, ir, ^{1}H nmr spectroscopy and ms. The analytical data of chemicals were in agreement with the proposed structures.

The ir spectra of compounds show absorption bands in the region of 1520, 1490, 1385, 1235, 1040 and 865, which is typical of 1,3,4-thiadiazole ring vibration [26]. In the mass spectra, the molecular ion peak was found to be present in most derivatives, however, with different relative intensity. Compound **X** lacks the molecular ion. The ^{1}H nmr spectral data show bands in the range 10.8-11.5 and 9.9-10.2 ppm characteristic of 2-COH and 4-COH protons in the resorcinol moiety respectively.

Concluding, the synthesis of 5-differently substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles has been described. The methodology presented herein is expected to be quite general for the synthesis of a very wide range of compounds with 2,4-dihydroxyphenyl moiety, substitution bladder cancer, A549 – non-small lung cancer, T47D-breast cancer) at the level of cisplatin, and exhibit antimycotic effects compared to those of commonly applied antifungal drugs. Therefore some attempts will be made to prepare a large number of derivatives as compounds with antifungal and antiproliferative activities.

EXPERIMENTAL

The melting point was determined using a Sanyo melting point apparatus. The elemental analysis was performed in order to determine C, H and N contents (Perkin-Elmer 2400). Analyses (C, N, H) were within ±0.4 % of the theoretical values. The oscillation spectra were recorded with a Perkin-Elmer FT-IR 1725X spectrophotometer (in potassium bromide). The spectra were made in the range of 600-4000 cm^{-1}. ^{1}H nmr spectra were made using the Bruker 500 MHz instrument, standard TMS, solutions in deuterio DMSO, shift δ (ppm). The spectra MS (EI-70 eV) were recorded using the apparatus AMD-604.

The purity of the compounds was examined by liquid chromatograph Knauer with a dual pump, a 20 µl simple injection valve and a UV-visible detector (330 nm). The Hypersil BDS C18 (5 µm, 150×4.6 mm) column was used as the stationary phase. The mobile phase consisted of different contents of methanol and acetate buffer (pH 4, 20 mM) as the aqueous phase. The flow rate was 0.5 ml/min at room temperature. The retention time of an unretained solute (t_0) was determined by the injection of a small amount of acetone dissolved in water. Log k values for 70% of methanol (v/v) in the mobile phase are presented.

Procedure for Preparation of Compounds (**I-X**).

2-(2,4-Dihydroxyphenyl)-5-phenyl-1,3,4-thiadiazole (**I**).

Benzhydrazide (0.01 mole) (Aldrich) and **STB** (0.0075 mole) were put into methanol (50 ml) and heated to boiling (3 h). The mixture was hot filtered. The filtrate was left at room temperature (24 h). The removed compound was recrystallized from methanol

(50 ml), mp 224-227°; hplc: log k=0.234; ^{1}H nmr (DMSO-d_6): δ 11.132 (s, H, 2-COH), 10.097 (s, H, 4-COH); ir (potassium bromide): 3112 (OH), 1632 (C=N), 1600 (C=C), 1527, 1461, 1436, 1328, 1255, 1180 (C-OH), 1140, 1113, 1072 (N=C-S-C=N), 1000, 984, 963, 916, 846 cm^{-1}; ms: m/z 270 (M$^+$, 100), 241 (2), 167 (30), 141 (2), 135 (19), 121 (7), 119 (3), 107 (3), 77 (6).

Anal. Calcd. for $C_{14}H_{10}N_2O_2S$ (270.31): C, 62.21; H, 3.73; N, 10.36. Found: C, 62.09; H, 3.72; N, 10.31.

2-(2,4-Dihydroxyphenyl)-5-(4-methylphenyl)-1,3,4-thiadiazole (**II**).

p-Toluic hydrazide (Aldrich) (0.01 mole) and **STB** (0.0075 mole) were put into methanol (50 ml) and heated to boiling (3 h). The mixture was hot filtered and the filtrate was concentrated to dry. The removed compound was washed with water and recrystallized from methanol (80 ml), mp 265-266°; hplc: log k=0.531; ^{1}H nmr (DMSO-d_6): δ 11.067 (s, H, 2-COH), 10.043 (s, H, 4-COH), 2.384 (s, 3H, CH_3,); ir (potassium bromide): 3132 (OH), 1633 (C=N), 1599 (C=C), 1529, 1456, 1324, 1257, 1177 (C-OH), 1140, 1020 (N=C-S-C=N), 996, 982, 963, 842, 810 cm^{-1}; ms: m/z 284 (M$^+$, 100), 255 (3), 167 (45), 153 (4), 149 (17), 135 (16), 118 (6), 107 (6), 91 (14).

Anal. Calcd. for $C_{15}H_{12}N_2O_2S$ (284.31): C, 63.36; H, 4.25; N, 9.85. Found: C, 63.51; H, 4.23; N, 9.82.

2-(2,4-Dihydroxyphenyl)-5-(3-hydroxyphenyl)-1,3,4-thiadiazole (**III**).

3-Hydroxybenzhydrazide (0.01 mole) (Lancaster) and **STB** (0.0075 mole) were put into methanol (50 ml) and heated to boiling (3 h). The mixture was hot filtered and the filtrate was concentrated to dry. The removed compound was washed with water and recrystallized from methanol (50 ml), mp 272-274°; hplc: log k=-0.208; ^{1}H nmr (DMSO-d_6): δ 11.093 (s, H, 2-COH), 10.057 (s, H, 4-COH), 9.818 (s, H, 3-COH); ir (potassium bromide): 3336 (OH), 1631 (C=N), 1599 (C=C), 1528, 1471, 1442, 1323, 1282, 1264, 1214, 1180 (C-OH), 1139, 986, 968, 864 cm^{-1}; ms: m/z 286 (M$^+$, 100), 257 (2), 167 (33), 153 (5), 151 (13), 137 (6), 119 (8), 107 (5), 93 (3), 80 (3), 65 (5), 52 (4), 39 (5).

Anal. Calcd. for $C_{14}H_{10}N_2O_3S$ (286.31): C, 58.73; H, 3.52; N, 9.78. Found: C, 58.59; H, 3.53; N, 9.74.

2-(2,4-Dihydroxyphenyl)-5-(4-hydroxyphenyl)-1,3,4-thiadiazole (**IV**).

4-Hydroxybenzhydrazide (Sigma) (0.01 mole) and **STB** (0.0075 mole) were put into methanol (50 ml) and heated to boiling (3 h). The mixture was hot filtered and the filtrate was concentrated to dry. The removed compound was washed with water and recrystallized from methanol (50 ml), mp 282-284°; hplc: log k=0.228; ^{1}H nmr (DMSO-d_6): δ 11.161 (H, 2-COH, s), 10.066 (s, H, 4-COH), 10.015 (s, H, 4-COH); ir (potassium bromide): 3349 (OH), 1632 (C=N), 1608 (C=C), 1524, 1451, 1426, 1332, 1255, 1176 (C-OH), 1140, 1100, 995, 984, 964 cm^{-1}; ms: m/z 286 (M$^+$, 100), 257 (3), 244, 229, 213, 197, 187, 184, 167 (48), 151 (26), 137 (14), 125 (2), 119 (15), 107 (7), 96 (3), 91 (3), 80 (5), 65 (9), 52 (5), 45 (2), 39 (7).

Anal. Calcd. for $C_{14}H_{10}N_2O_3S$ (286.31): C, 58.73; H, 3.52; N, 9.78. Found: C, 58.57; H, 3.53; N, 9.74.

2-(2,4-Dihydroxyphenyl)-5-(1-naphthyl)-1,3,4-thiadiazole (**V**).

1-Naphthyhydrazide (Lancaster) (0.01 mole) and **STB** (0.0075 mole) were put into methanol (50 ml) and heated to boiling (3 h). The mixture was hot filtered and water (100 ml) was added to the filtrate. The filtrate was left at room temperature (24 h). The removed compound was filtered, washed with water and recrystallized from diluted (5:1) methanol (60 ml), mp 150-152°; hplc: log k=0.576; ^{1}H nmr (DMSO-d_6): δ 11.176 (s, H, 2-COH), 10.092 (s, H, 4-COH); ir (potassium bromide): 3175 (OH), 1630 (C=N), 1596 (C=C), 1524, 1510, 1471, 1445, 1314, 1218 (C-OH), 1169, 1136, 1109, 1024 (N=C-S-C=N), 986, 968, 940, 846, 801 cm^{-1}; ms: m/z 320 (M$^+$, 53), 304 (5), 291 (2), 286, 275, 256 (1), 247 (1), 202, 185 (100), 171 (6), 160 (4), 153 (15), 137 (10), 127 (13), 119 (2), 107 (2), 97 (2), 77 (2), 69 (3), 63 (92), 52 (3), 39 (3).

Anal. Calcd. for $C_{18}H_{12}N_2O_2S$ (320.37): C, 67.48; H, 3.79; N, 8.74. Found: C, 67.25; H, 3.78; N, 8.69.

2-(2,4-Dihydroxyphenyl)-5-benzyl-1,3,4-thiadiazole (**VI**).

Phenylacetic acid hydrazide (0.01 mole) (Sigma) and **STB** (0.0075 mole) were put into methanol (50 ml) and heated to boiling (3 h). The mixture was hot filtered and the filtrate was concentrated to dry. The removed compound was washed with water and recrystallized from diluted (3:1) methanol (60 ml), mp 156-158°; hplc: log k=0.017; ^{1}H nmr (DMSO-d_6): δ 10.897 (s, H, 2-COH), 9.982 (s, H, 4-COH), 4.442 (s, 2H, CH_2); ir (potassium bromide): 3226 and 3024 (OH), 2931 (C_{alif}-H), 1608 (C=N, C=C), 1522, 1494, 1742, 1420, 1347, 1320, 1272, 1213, 1186 (C-OH), 1136, 1123, 1093, 1029 (N=C-S-C=N), 989, 968, 926, 867, 845, 818, 811 cm^{-1}; ms: m/z 284 (M$^+$, 100), 255 (3), 167 (4), 153 (4), 149 (61), 135 (7), 122 (14), 116 (6), 107 (5), 91 (23), 80 (4), 65 (7), 52 (6), 39 (7).

Anal. Calcd. for $C_{15}H_{12}N_2O_2S$ (284.34): C, 63.36; H, 4.25; N, 9.85. Found: C, 63.21; H, 4.27; N, 9.84.

2-(2,4-Dihydroxyphenyl)-5-(4-fluorophenoxymethyl)-1,3,4-thiadiazole (**VII**).

2-(4-Fluorophenoxy)acetic acid hydrazide (0.01 mole) (Aldrich) and **STB** (0.0075 mole) were put into methanol (50 ml) and heated to boiling (3 h). The mixture was hot filtered. The removed compound was washed with water and recrystallized from diluted (1:1) methanol (75 ml), mp 138-140°; hplc: log k=0.119; ^{1}H nmr (DMSO-d_6): δ 11.145 (s, H, 2-COH), 10.195 (s, H, 4-COH), 5.559 (s, 2H, CH_2); ir (potassium bromide): 3118 (OH), 1619 (C=N), 1506 (C=C), 1453, 1419, 1369, 1334, 1292, 1221 (C-OH), 1135, 1097, 1041 (N=C-S-C=N), 981, 886 cm^{-1}; ms: m/z 318 (M$^+$, 12), 289, 225 (1), 207 (100), 197, 178 (3), 167 (7), 153 (85), 135 (5), 125 (7), 112 (10), 107 (3), 95 (10), 83 (11), 69 (5), 57 (6), 51 (4), 39 (6).

Anal. Calcd. for $C_{15}H_{11}FN_2O_3S$ (318.32): C, 56.60; H, 3.48; N, 8.80. Found: C, 56.48; H, 3.47; N, 8.81.

2-(2,4-Dihydroxyphenyl)-5-(4-pyridyl)-1,3,4-thiadiazole (**VIII**).

4-Pyridinecarboxylic acid hydrazide (Merck) (0.01 mole) and **STB** (0.0075 mole) were put into DMSO (50 ml) and heated to boiling (3 h). The mixture was hot filtered and 50 ml of water were added to the filtrate. The removed compound was recrystallized from diluted (2:1) methanol (70 ml), mp 305-307°; hplc: log k=-0.374; ^{1}H nmr (DMSO-d_6): δ 11.291 (s, H, 2-COH), 10.178 (s, H, 4-COH), 8.766-8.751 (m, 2H, $NC_{pyr}H$), 7.956-7.966 (m, 2H, $C_{pyr}H$); ir (potassium bromide): 3044 (OH), 2931, 2786, 1597 (C=N), 1557 (C=C), 1516, 1474, 1426, 1335, 1288, 1212, 1195 (C-OH), 1132, 1109, 1068 (N=C-S-C=N), 1017, 1003, 985, 975, 952, 876, 814 cm^{-1}; ms: m/z 271 (M$^+$, 100), 242 (3), 214 (1), 167 (44), 153 (8), 139 (3), 135 (17), 122 (10), 107 (10), 95 (3), 78 (13), 69 (8), 63 (5), 51 (17), 39 (10).

Anal. Calcd. for $C_{13}H_9N_3O_2S$ (271.30): C, 57.55; H, 3.34; N, 15.49. Found: C, 57.28; H, 3.35; N, 15.42.

2-(2,4-Dihydroxyphenyl)-5-ethoxy-1,3,4-thiadiazole (**IX**).

Ethyl carbazate (0.01 mole) (Aldrich) and **STB** (0.0075 mole) were put into methanol (50 ml) and heated to boiling (3 h). The mixture was hot filtered, 100 ml of water were added to the filtrate and it was left at room temperature (24 h). The removed compound was filtered, washed with water and recrystallized from diluted (5:1) methanol (60 ml), mp 163-165°; hplc: log k=0.157; ^{1}H nmr (DMSO-d_6): δ 11.543 (s, H, 2-COH), 10.198 (s, H, 4-COH), 4.130-4.078 (q, 2H, CH_2), 1.244-1.196 (m, 3H, CH_3); ir (potassium bromide): 3264 (OH), 1695 (C=N), 1614, 1593 (C=C), 1504, 1462, 1406, 1371, 1341, 1321, 1302, 1255, 1184 (C-OH), 1122, 1044 (N=C-S-C=N), 986, 948, 865, 809 cm^{-1}; ms: m/z 238 (M^+, 5), 222 (3), 210 (100), 194 (7), 181 (2), 167 (4), 161 (3), 153 (29), 137 (17), 124 (5), 121 (16), 108 (8), 94 (32), 81 (11), 66 (26), 52 (12), 44 (17), 39 (17).

Anal. Calcd. for $C_{10}H_{10}N_2O_3S$ (238.27): C, 50.41; H, 4.23; N, 11.76. Found: C, 50.72; H, 4.25; N, 11.55.

2-(2,4-Dihydroxyphenyl)-5-(4-methoxybenzyloxy)-1,3,4-thiadiazole (**X**).

4-Methoxybenzyl carbazate (0.01 mole) (Sigma) and **STB** (0.0075 mole) were put into methanol (50 ml) and heated to boiling (3 h). The mixture was hot filtered and water (100 ml) was added to filtrate. The removed compound was filtered, washed with water and recrystallized from diluted (3:1) methanol (80 ml), mp 134-135°; hplc: log k=-0.307; ^{1}H nmr (DMSO-d_6): δ 11.541 (s, H, 2-COH), 10.163 (s, H, 4-COH), 5.068 (s, 2H, CH_2), 3.754-3.704 (m, 3H, CH_3); ir (potassium bromide): 3260, 3057 (OH), 2963 and 2835 (CH_3), 1691 (C=N), 1616, 1597 C=C, 1505, 1460, 1419, 1346, 1319, 1250, 1178 C-OH, 1125, 1028 (N=C-S-C=N), 964, 927, 862 cm^{-1}; ms: m/z 302 (10), 286, 273 (4), 184, 167 (33), 153 (11), 136 (7), 121 (10), 107 (4), 97 (1), 80 (3), 69 (2), 52 (3), 39 (2).

Anal. Calcd. for $C_{16}H_{14}N_2O_4S$ (330.36): C, 58.17; H, 4.27; N, 8.48. Found: C, 58.47; H, 4.26; N, 8.44.

REFERENCES AND NOTES

[1] D. L. Hill, *Cancer. Chemother. Pharmacol*., **4**, 215 (1980).

[2] G. Palaska, P. Şahin, N. T Kelicen, G. Dyrlu and G. Altinok, *Farmaco*, **57**, 101 (2002).

[3] H. N. Dogan, A. Duran, S. Rollas, G. Sener, M. K. Uysal and D. Gülen, *Bioorg. Med. Chem.*, **10**, 2893 (2002).

[4] S. Karakuş and S. Rollas, *Farmaco*, **57**, 577 (2002).

[5] A. Foroumadi, A. Asadipour, M. Mirzaei, J. Karimi and S. Emami, *Farmaco*, **57**, 765 (2002).

[6] K. Zamani, K. Faghihi, M. R. Sangi and J. Zolgharnein, *Turk. J. Chem.*, **27**, 119 (2003).

[7] S. M. Golovlyova, Y.A. Moskvichev, E. M. A. Alov, D.B. Kobylinsky and V.V. Ermolaeva, *Chem. Heterocycl. Comp*., **37**, 1102 (2001).

[8] T.R. Hovsepian, E. D. Dilanian, A. P. Engoyan and R. G. Melik-Ohanjanian, *Chem. Heterocycl. Comp*., **40**, 1194 (2004).

[9] X. Wang, Z. Li, Y. Da and B. Wei, *Synth. Commun.*, **31**, 2537 (2001).

[10] X. Wang, Z. Li, and Y. Da, *Synth. Commun*., **31**, 19 (2001).

[11] G. Werber, F. Buccheri, M. Gentile and L. Librici, *J. Heterocycl. Chem*., **14**, 853 (1977).

[12] R. Noto, F. Buccheri, G. Cusmano, M. Gruttadauria and G. Werber, *J. Heterocycl. Chem*., **28**, 1421 (1991).

[13] R. Noto, M. Gruttadauria, P. Lo Meo and G. Werber, *J. Heterocycl. Chem*., **33**, 863 (1996).

[14] J.P. Kilburn, J. Lau and R.C.F. Jones, *Tetrahedron Lett*., **44**, 7825 (2003).

[15] V. N. Yarovenko, A. V. Shirokov, O. N. Krupinova, I. V. Zawarzin and M. M. Krayushkin, *Russ. J. Org. Chem*., **39**, 1133 (2003).

[16] S. Kubota, Y. Koida, T. Kosaka and O. Kirino, *Chem. Pharm. Bull*., **18**, 1696 (1970).

[17] B. H. Lee, F. D. Dutton, M. F. Clothier, J. W. Bowman, J. P. Davis, S. S. Johnson, E. M. Thomas, M. R. Zantello, E. W. Zinser, J. C. McGuire, D. P. Thompson and T.G. Geary, *Bioorg. Med. Chem. Lett.*, **9**, 1727 (1999).

[18] B. Modzelewska-Banachiewicz, E. Jagiełło-Wójtowicz and E. Tokarzewska-Wielosz, *Acta Polon. Pharm.–Drug. Res*. **57**, 199 (2000).

[19] A. Niewiadomy, J. Matysiak and G. Mącik-Niewiadomy, PL Patent pending 330263A1 (2000).

[20] B. Modzelewska-Banachiewicz, J. Matysiak and A. Niewiadomy, *Eur. J. Med. Chem*., **36**, 75 (2001).

[21] A. Niewiadomy, J. Matysiak and G. Mącik-Niewiadomy, *Eur. J. Pharm. Sci*., **13**, 243 (2001).

[22] J. Matysiak and A. Niewiadomy, *Bioorg. Med. Chem*. **11**, 2285 (2003).

[23] J. Legocki, J. Matysiak, A. Niewiadomy and M. Kostecka, *J. Agric. Food Chem.*, **51**, 362 (2003).

[24] O. Baine, G. F. Adamson, J. W. Barton, J. L. Fitch, D. R. Swayampati and H. Jeskey, *J. Org. Chem.*, **19**, 510 (1954).

[25] P. E. Allegretti, E. A. Castro and J. P. J. Furlong, *J. Mol. Struct. (Theochem)*, **499**, 121 (2000).

[26] Katritzky, A. R. (Editor) Physical Methods in Heterocyclic Chemistry. New York, Academic Press, 1963.