Synthesis of some Pyrazolo[1,5-*c*][1,3]benzoxazines and a New 5*H*-Pyrazolo[1,5-*c*][1,3,2]benzoxazaphosphorine Ring system

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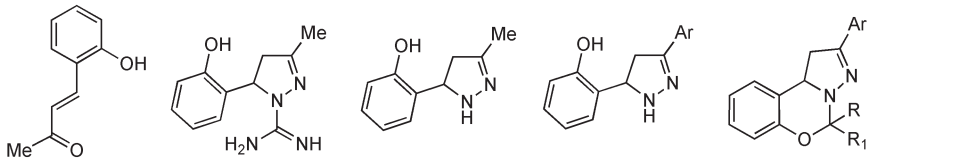
Received January 14, 2005

Condensations of 5-(2-hydroxyphenyl)pyrazoline **3a** with 4-carboxybenzaldehyde, glyoxylic acid and *N*,*N*'-carbonyldiimidazole leading to pyrazolobenzoxazine derivatives were studied. The observed diastereoselectivity is discussed. Reaction of **3a** with Lawesson reagent gave rise to a new 5*H*-pyrazolo[1,5-*c*]-[1,3,2]benzoxazaphosphorine heterocyclic system.

J. Heterocyclic Chem., **42**, 1143 (2005).

As a continuation of our research on the application of 4-(2-hydroxyphenyl)but-3-en-2-one (**1**) in heterocyclic synthesis we described a facile route to hydroxyphenylpyrazoline **2** [1]. The behaviour of the appropriately substituted pyrazoline was subsequently examined in ring closure reactions [2]. To exploit these studies, we directed our interest towards a simpler analogue **3a**, which lacks the amidine moiety on the nitrogen ring atom N-1. This compound is readily accessible from synthon **1** and hydrazine [3]. Analogously, 3-aryl or 3-hetaryl congeners **3b** can be prepared from the corresponding chalcones [4]. The bifunctional nature of pyrazolines **3** together with a favourable arrangement of the reaction centres make them capable of forming an additional fused six-membered heterocycle. This was demonstrated by heterocyclizations of synthons **3b** with aldehydes, ketones [5,6] and phosgene [7] or triphosgene [8] which in each case led to 1,10b-dihydro-5*H*-pyrazolo[1,5-*c*][1,3]benzoxazines **4** (Scheme 1).

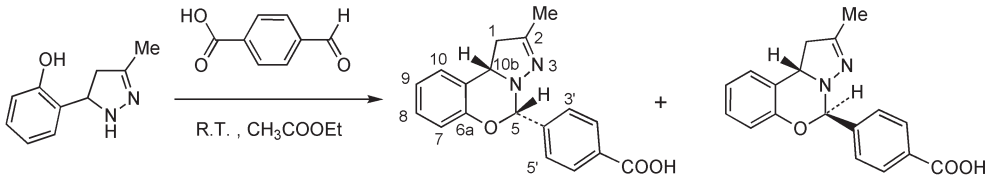


1 **2** **3a** **3b**: Ar = aryl **4**: R, R_1 = alkyl, aryl, H, =O

Due to their diverse biological activities, 2-pyrazolines became an attractive pharmaceutical target [4]. In addition, certain 2-pyrazolines have been discovered to significantly inhibit both pathways of arachidonate metabolism [9,10], a feature that is of importance for novel cyclooxygenase inhibitors (COX-2) [11]. Besides being effective antiinflammatory drugs [12], COX-2 inhibitors can be used to treat various cancers [13], and also for prevention of neurodegenerative disorders such as Alzheimer's disease [14]. To meet pharmaceutical needs for continuing activity testing in the aforementioned therapeutic groups, we describe here the preparation of some derivatives related to the ring system **4**. A particular emphasis in drug development has been put on target solubility and proper transport properties in physiological systems. Furthermore, a new phosphorus heterocycle being elaborated from **3a** is presented.

To obtain water-soluble derivatives, we chose aldehydes bearing a carboxyl function, *e.g.* 4-carboxybenzaldehyde (4-formylbenzoic acid), to be used in cyclocondensation with **3a**. The reaction proceeded easily and cleanly at room temperature and the desired product **5** began to precipitate within a few minutes. According to the ^{1}H nmr (DMSO-d_6), the obtained tricycle exists as a mixture of two diastereoisomers, *cis*-**5** and *trans*-**5**, in a 53:47 ratio (Scheme 2). The ^{1}H nmr spectrum consisted of two simi-

lar, mostly well resolved, sets of ^{1}H resonances. The respective chemical shifts of the diagnostic methines at chiral centres C-5 and C-10b and those of the carboxyphenyl substituent differed substantially from each other in both isomers. The methyl group displayed a pair of near but separated singlets whereas corresponding signals of methylene protons 1-H_a and 1-H_b (AB region of the ABX system) revealed no pairing pattern. The assignment

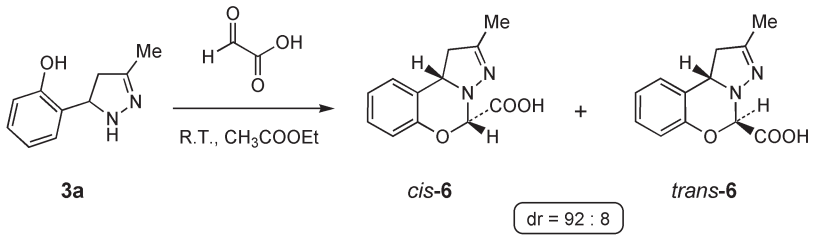


3a *cis*-**5** *trans*-**5**

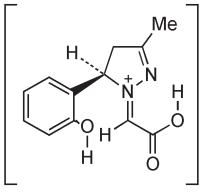
to either form was achieved with the aid of NOE experiments. For *cis*-**5**, strong NOE interactions were detected between 5-H_{ax} – 10b-H_{ax} and 5-H_{ax} – 3'-H_{arom} + 5'-H_{arom}. A similar spatial relationship was found between the axial aliphatic methines in analogous 2,5-diarylpyrazolobenzoxazines [6]. Isomer *trans*-**5** showed NOE enhancements for *meta*-protons 3'-H and 5'-H (to COOH) when the signal of proximal 10b-H_{ax} proton was selectively saturated.

Glyoxylic acid seemed to be another suitable reactant for our purposes. Cyclocondensation occurred again under mild conditions in ethyl acetate using 50 % water solution of the acid. Surprisingly, the target product **6**, which was isolated as a precipitate and then as a crystalline material from the filtrate, was a pure single diastereoisomer. On the basis of 1D differential NOE, both 5-H and 10b-H protons were found to be axial and thus the carboxyl was in an equatorial position. Consequently, the relative configuration of the dominant form was established to be (5*S**,10b*S**), *i.e.* *cis*-**6** (Scheme 3). The CH_2CH fragment in the pyrazoline ring was expected to constitute an ABX system. However, the lower field A proton of the AB pair appeared as a characteristic doublet of doublet pattern with an additional fine quartet splitting. This small coupling is due to a four-bond interaction with the methyl protons. Therefore, the ABM_3X spin notation should be used to classify these nuclei correctly. Since long-range couplings in general occur effectively in a planar zig-zag arrangement [15], one can expect that the A proton should have a pseudoequatorial orientation. However, the observed vicinal coupling constants (J_{AX} = 9.6 and J_{BX} = 0 Hz) together with NOE enhancement for A and X protons point to its cisoid and pseudoaxial orientation, as well. The zero value of $^3J_{BX}$, indicating a dihedral angle between B and X close to 90°, also supports the proposed configuration of the 1-H_a, 1-H_b, and 10b-H hydrogen atoms. Indeed, it is rather unusual that the four-bond coupling of 1-H_a with Me occurred along a nonplanar path of interacting nuclei.

In addition, we also obtained a small quantity of another isomer, *trans*-**6** (5*R**,10b*S**) (Scheme 3). The diastereoisomers *cis*-**6** and *trans*-**6** were formed in a 92:8 ratio with a total yield of 66 %. ^{1}H nmr (DMSO-d_6) showed that *cis*-**6** epimerized only partially into *trans*-**6**, as the unchanged *cis* isomer was still present at 65 % after seven days. The pronounced predominance of the *cis*-carboxylic acid **6** in the cyclization product and its lower content at equilibrium indicated that the reaction stereochemistry was controlled kinetically. The high diastereoselectivity can be explained by a simple model, which is outlined in Figure 1. We presume that the reaction proceeds through the formation of a non-cyclic iminium species **I** with *Z* configuration at the exocyclic imine double bond. This intermediate may benefit from a stabilizing hydrogen bond interaction between the carboxyl OH group and the adjacent pyrazoline nitrogen atom N-2. Following a nucleophilic attack by phenolic hydroxyl at the iminium carbon from the front side in the postulated structure **I**, the COOH group would assume an equatorial position on the benzoxazine ring, thus giving the *cis*-**6** isomer. Therefore, the hydrogen bond stabilization of the exocyclic C=N bond geometry can be considered as a decisive factor for the observed stereoselectivity.



3a *cis*-**6** *trans*-**6**



I

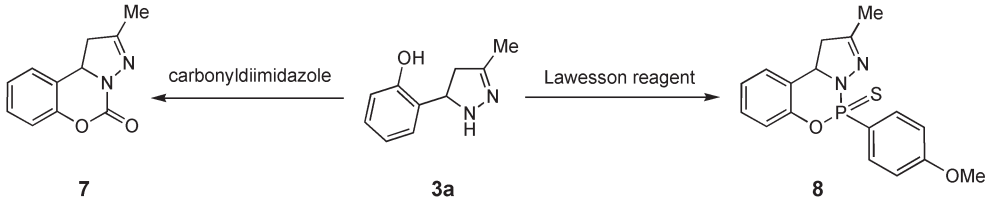
As to benzoic acid derivatives **5**, molecular mechanics calculations showed that epimers *cis*-**5** and *trans*-**5** have very similar enthalpies. A small difference from these calculations, ΔH°_{298} *cis*→*trans*: 0.23 kcal/mol, appears to be compatible with the 53:47 isomer ratio. These isomer populations can be attributed to either a low diastereoselectivity or fast equilibration after the reaction. Note that acidic carboxyl group in compound **5**, 4-substituted benzoic acid, can catalyze the isomerization as described previously [6]. Thus, an autocatalytic process might take place in this case.

Another possibility for introducing a polar group into our substrate **3a** during the heterocyclization step was based on the known reaction of pyrazolines **3b** with phosgene [7,8]. In contrast to the reported procedure, we used *N*,*N*'-carbonyldiimidazole (CDI) as a carbonyl equivalent and a safer reagent than $COCl_2$. Upon treatment of pyrazoline **3a** with CDI in refluxing benzene for 200 min we obtained the required pyrazolo[1,5-*c*][1,3]benzoxazin-5-one **7** in very good yield (Scheme 4). Cyclization can also be accomplished in a similar yield by reflux in dichloromethane, although at a considerably longer time (9 hr). The spectroscopic data for product **7** are in accordance with the proposed structure. For example, the absorption band found for the C=O stretching vibration (ν 1758 cm^{-1}) fits well the wave numbers reported for similar cyclic carbamates [7]. The pyrazoline fragment in **7** also gave the ABM_3X spin system in the ^1H nmr spectrum. In contrast to compound **6**, the higher field resonance in the AB region belonging to the B proton in **7** revealed a long-range coupling with the methyl protons. With regard to NOE between 10b-H_{ax} and A, the B proton in **7** has to face an opposite side of pyrazoline ring and it is likely in a pseudoaxial position (J_{AX} = 10.2, J_{BX} = 12.9 Hz).

The Lawesson reagent is known not only as a powerful thionation reagent but also by its ability to produce phosphorus heterocycles [16]. It is capable to react with both amines and alcohols or phenols [16]. As shown, the presence of these functionalities in pyrazoline **3a** is ideal for such an elaboration to build up a 6-membered O,P,N-core. These transformations are usually performed in refluxing aromatic hydrocarbons. We found that the best conditions for a successful heterocyclization are refluxing in toluene for 150 min with 0.55 equivalents of the reagent. The desired product **8** (Scheme 4) was isolated in a 30 % yield after purification by column chromatography.

The expected ring closure was corroborated by mass spectrometry which showed a molecular ion M^+ at *m/z* 344 as the second most abundant peak in the mass spectrum. ^{31}P nmr spectroscopy provided further evidence for the proposed structure **8**. The chemical shift of the tetracovalent phosphorus (V) at $\delta_P\{H\}$ 72.3 matches the values that were found in the range of 67-77 ppm for similar 1,3,2-oxazaphosphorin-2-sulfides [17] or their benzologs [18]. Moreover, three- and four-bond ^{31}P-^1H couplings [^3J(P,10b-H), ^4J(P,1a-H), ^4J(P,1b-H)] along with two- and three-bond ^{31}P-^{13}C couplings [^2J(P,C-6a), ^3J(P,C-1), ^3J(P,C-2), ^3J(P,C-7), ^3J(P,C-10a)] that were observed in the ^1H and ^{13}C nmr spectra also supported phosphorus atom bonding to both pyrazoline and phenolic moieties.

The 2,5-disubstituted 1,10b-dihydro-5*H*-pyrazolo[1,5-*c*]-[1,3,2]benzoxazaphosphorin-5-sulfide prepared here represents a new class of polycondensed heterocycles. Considering that some 1,3,2-benzoxazaphosphorines exhibit interesting anticancer [19] and neuroleptic [20] properties and act as antiserotoninergic drugs [20], derivative **8** might be a valuable bioactive molecule.



7 **3a** **8**

EXPERIMENTAL

The melting points (uncorrected) were determined with a Kofler hot stage microscope. The ir spectra were recorded on a Nicolet Impact 400 D spectrophotometer. The EI mass spectra were obtained on a Jeol JMS D-100 instrument operating at 75 eV. The nmr spectra were measured on a Varian VXR-300 spectrometer with a dual $^1H/^{13}C$ probe (299.943 MHz for ^1H and 75.429 MHz for ^{13}C).

4-(1,10b-Dihydro-2-methyl-5*H*-pyrazolo[1,5-*c*][1,3]benzoxazin-5-yl)benzoic Acid (*cis*-**5** and *trans*-**5**).

To a solution of 4-carboxybenzaldehyde (0.30 g, 2 mmoles) in ethyl acetate (14 ml) and methanol (1 ml) was added pyrazoline **3a** (0.352 mg, 2 mmoles) under stirring at room temperature. During 5-10 minutes the product began to precipitate. After 1 hour the separated solid was collected and washed with ether. Compound **5** was obtained in 70 % yield (0.43 g), mp.207-210° dec (EtOH); ir (potassium bromide): 1698 (COOH), 1613 (C=N), 1233 (C-O-C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.73 (s, *cis* Me), 1.86 (s, *trans* Me), 2.73 (m, *cis* + *trans* 1-H_b), 3.20 (m, *cis* + *trans* 1-H_a), 4.56 (d, J_{AX}=9.0 Hz, *trans* 10b-H), 5.18 (d, J_{AX}=9.0 Hz, *cis* 10b-H), 6.16 (s, *cis* 5-H), 6.72 (s, *trans* 5-H), 6.81-7.21 (m, *cis* + *trans* 7-, 8-, 9-, 10-H), 7.61 (d, *trans* 3'-H + 5'-H), 7.75 (d, *cis* 3'-H + 5'-H), 7.91 (d, *trans* 2'-H + 6'-H), 8.05 (d, *cis* 2'-H + 6'-H), 12.98 (br s, *cis* + *trans* COOH).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.97; H, 5.44, N, 9.01.

1,10b-Dihydro-2-methyl-5*H*-pyrazolo[1,5-*c*][1,3]benzoxazin-5-carboxylic Acid (**6**).

To a solution of pyrazoline **3a** (1.50 g, 8.5 mmoles) in ethyl acetate (25 ml) was added 50 % aqueous glyoxylic acid (1.5 ml, 13.5 mmoles). The reaction mixture was stirred for 24 hours at room temperature. The precipitated product *cis*-**6** was collected by filtration (0.69 g). The filtrate was evaporated and the yellowish oil was dissolved in a small volume of ethyl acetate/ether and allowed to crystallize. A further crop of *cis*-**6** was obtained (0.51 g). The second isomer *trans*-**6** crystallized then from the mother liquor (0.1 g). Compound **6** was isolated in 66 % total yield (1.21 g); (5*S**,10b*S**) isomer mp. > 152° dec (CH_3COOEt); ir (potassium bromide): 1724 (COOH), 1228 (C-O-C) cm^{-1}; ^1H nmr (acetone-d_6): δ 1.84 (d, 3H, J_{AMe}=1.2 Hz, Me), 2.80 (d, 1H, J_{AB}=16.5 Hz, 1-H_b), 3.28 (ddq, 1H, J_{AB}=16.5, J_{AX}=9.6, J_{AMe}=1.2 Hz, 1-H_a), 5.13 (d, 1H, J_{AX}=9.6 Hz, 10b-H), 5.50 (s, 1H, 5-H), 6.81 (dd, 1H, 7-H), 7.01 (td, 1H, 9-H), 7.14-7.17 (m, 2H, 8-H + 10-H); ^{13}C nmr (methanol-d_4 + chloroform-d_1): δ 16.1 (Me), 46.1 (CH_2), 59.2 (CH-10b), 84.0 (CH-5), 117.7 (CH-7), 123.0 (CH-9), 124.1 (C-10a), 126.9 (CH-10), 128.4 (CH-8), 153.0 (C-6a), 157.5 (C=N), 168.0 (COOH).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.31; H, 5.32; N, 11.93.

The (5*R**,10b*S**) isomer has mp. > 147° dec (CH_3COOEt); ir (potassium bromide): 1719 (COOH), 1199 (C-O-C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.82 (d, 3H, J_{AMe}=1.2 Hz, Me), 2.74 (d, 1H, J_{AB}=17.1 Hz, 1-H_b), 3.24 (ddq, 1H, J_{AB}=17.1, J_{AX}=9.3, J_{AMe}=1.2 Hz, 1-H_a), 4.83 (d, 1H, J_{AX}=9.3 Hz, 10b-H), 5.94 (s, 1H, 5-H), 6.73 (dd, 1H, 7-H), 6.91 (td, 1H, 9-H), 7.06 (dd, 1H, 10-H), 7.10 (td, 1H, 8-H).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.87; H, 5.39; N, 12.33.

1,10b-Dihydro-2-methyl-5*H*-pyrazolo[1,5-*c*][1,3]benzoxazin-5-one (**7**).

A solution of pyrazoline **3a** (0.352 g, 2 mmoles) and *N*,*N*'-carbonyldiimidazole (0.356 g, 2.2 mmoles) in benzene (15 ml) was refluxed for 200 minutes. After removal of the solvent the oily residue was dissolved in dichloromethane (25 ml), washed with 10 % HCl (2 x 10 ml), water (1 x 10 ml) and dried ($MgSO_4$). The solution was concentrated under reduced pressure to give a solid. After washing with ether (5 ml) compound **7** was obtained in 90 % yield (0.365 g), mp. 160-161° (CH_3COOEt); ir (potassium bromide): 1758 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.18 (s, 3H, Me), 3.11 (ddq, 1H, J_{AB}=16.8, J_{BX}=12.9, J_{BMe}=1.2 Hz, 1-H_b), 3.38 (dd, 1H, J_{AB}=16.8, J_{AX}=10.2 Hz, 1-H_a), 5.28 (dd, 1H, J_{BX}=12.9, J_{AX}=10.2 Hz, 10b-H), 7.09-7.22 (m, 3H, 7-H + 9-H + 10-H), 7.33 (td, 1H, 8-H); ^{13}C nmr (chloroform-d_1): δ 16.2 (Me), 42.4 (CH_2), 57.1 (CH-10b), 116.7 (CH-7), 122.7 (C-10a), 124.7, 124.9 (CH-10 + CH-9), 129.6 (CH-8), 146.4 (N-C=O), 150.3 (C-6a), 159.9 (C=N); m/s : *m/z* (relative intensity) 202 (M^+, 80), 185 (6), 173 (5), 161 (36), 145 (28), 131 (34), 127 (5), 123 (4), 119 (17), 111 (5), 104 (9), 97 (8), 91 (20), 83 (66), 77 (21), 69 (37), 63 (24), 60 (7), 55 (100), 51 (36), 41 (27), 39 (41).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.41; H, 4.89; N, 13.78.

1,10b-Dihydro-5-(4-methoxyphenyl)-2-methyl-5*H*-pyrazolo[1,5-*c*][1,3,2]benzoxazaphosphorin-5-sulfide (**8**).

To a solution of pyrazoline **3a** (0.352 g, 2 mmoles) in warm benzene (25 ml) was added Lawesson reagent (0.405 g, 1 mmol) in one portion. The reaction mixture was stirred and refluxed under nitrogen for 2 hours. The solution was concentrated *in vacuo* to give a semisolid which was dissolved in minimal volume of $CHCl_3$. Chromatography on silica gel ($CHCl_3$/AcOEt 1:1) and treatment of the corresponding fraction with AcOEt (R_f=0.61 in AcOEt) gave product **8** in 30 % yield (0.235 g), mp. 184-186° (MeCN); ir (potassium bromide) 1596, 1500, 1484, 1449, 1260, 1175, 1120, 1100, 1028, 894, 829, 806, 790 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.05 (d, 3H, J_{AMe}=1.0 Hz, Me), 3.17 (ddd, 1H, J_{AB}=17.0, J_{BX}=9.1, J_{PB}=1.1 Hz, 1-H_b), 3.34 (dddq, 1H, J_{AB}=17.0, J_{AX}=11.1, J_{PA}=2.6, J_{AMe}=1.0 Hz, 1-H_a), 3.84 (s, 3H, OMe), 5.18 (ddd, 1H, J_{AX}=11.1, J_{BX}=9.1, J_{PX}=3.2 Hz, 10b-H), 6.96 (dd, 2H, J_{HH}=9.0, J_{PH}=3.4 Hz, H-3' + H-5'), 7.09 (dm, 1H, J=7.5 Hz, 7-H), 7.13 (dm, 1H, J=8.1 Hz, 10-H), 7.16 (tm, 1H, J=7.5 Hz, 9-H), 7.31 (tm, 1H, J=8.1 Hz, 8-H), 7.91 (dd, 2H, J_{PH}=14.1, J_{HH}=8.7 Hz, H-2' + H-6'); ^{13}C nmr (DMSO-d_6): δ 15.9 (Me), 43.6 (CH_2, $^3J_{PC}$=2.9 Hz), 55.4 (OMe), 59.3 (CH-10b), 114.0 (CH-3' + CH-5' , $^3J_{PC}$=16.2 Hz), 119.8 (CH-7, $^3J_{PC}$=6.0 Hz), 124.6 (CH-9), 124.7 (C-1', $^1J_{PC}$=149.5 Hz), 125.8 (CH-10), 128.3 (C-10a, $^3J_{PC}$=9.3 Hz), 129.3 (CH-8), 133.2 (CH-2' + CH-6', $^2J_{PC}$=13.9 Hz), 149.3 (C-6a, $^2J_{PC}$=9.2 Hz), 156.2 (C=N, $^3J_{PC}$=15.2 Hz), 162.99 (C-4', $^4J_{PC}$=3.1 Hz); ^{31}P nmr (DMSO-d_6):δ 72.3 (O-P(=S)-N); m/s : *m/z* (relative intensity) 345 (M^+ + 1, 31), 344 (M^+, 96), 343 (100), 262 (36), 257 (27), 235 (42), 229 (19), 210 (16), 203 (19), 155 (25), 137 (8), 123 (8), 121 (9), 91 (8), 77 (18), 63 (21).

Anal. Calcd. for $C_{17}H_{17}N_2O_2PS$: C, 59.29; H, 4.98; N, 8.13. Found: C, 59.42; H, 5.13; N, 8.01.

Acknowledgements.

This work was supported by the Grant Agency of the Slovak Republic (# 1/1196/04 and 1/1167/04).

REFERENCES AND NOTES

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[1] J. Svetlik and L. Sallai, *J. Heterocyclic Chem.*, **39**, 363 (2002).

[2] J. Svetlik and T. Liptaj, *J. Chem. Soc., Perkin Trans 1*, 1260 (2002).

[3] I. I. Grandberg, V. P. Din and A. N. Kost, *Zh. Obshch. Khim*., **30**, 1373 (1960); *Chem. Abstr.*, **55**, 517i (1961).

[4] A. Levai, *J. Heterocyclic Chem.*, **39**, 1 (2002).

[5] V. D. Orlov, N. V. Getmanskii, I. A. Oksanich and S. V. Iksanova, *Khim. Geterotsikl. Soedin.*, 1131 (1991); *Chem. Abstr.*, **116**, 194239s (1992).

[6] S. M. Desenko, N. V. Getmanskii, V. N. Chernenko, I. M. Zemlin, O. V. Shishkin and V. D. Orlov, *Khim. Geterotsikl. Soedin.*, 805 (1999); *Chem. Abstr.*, **132**, 180531z (2000).

[7] G. A. M. Nawwar, *J. Chem. Research (S)*, 344 (1991).

[8] F. Varano, D. Catarzi, V. Colotta, L. Cecchi, G. Filacchioni, A. Galli and C. Costagli, *Arch. Pharm*., **329**, 529 (1996).

[9] G. A. Higgs, R. J. Flower and J. R. Vane, *Biochem. Pharmacol.*, **28**, 1959 (1979).

[10] F. C. Copp, P. J. Islip and J. E. Tateson, *Biochem. Pharmacol.*, **33**, 339 (1984).

[11] Y. Jahng, L. X. Zhao, Y. S. Moon, A. Basnet, E. Kim, H. W. Chang, H. K. Ju, T. C. Jeong and E. S. Lee, *Bioorg. Med. Chem. Lett.*, **14**, 2559 (2004).

[12] R. R. Ramatunge, M. Augustyniuk, U. P. Bandarage, R. A. Earl, J. L. Ellis, D. S. Garvey, D. R. Janero, L. G. Letts, A. M. Martino, M. G. Murty, S. K. Richardson, J. D. Schroeder, M. J. Shumway, S. W.

Tam, A. M. Trocha and D. V. Young, *J. Med. Chem.*, **47**, 2180 (2004).

[13] K. Subbaramaiah, L. Norton, W. Gerald and A. J. Dannenberg, *J. Biol. Chem.*, **277**, 18649 (2002).

[14] G. M. Pasinetti, *Arch. Gerontol. Geriatr.*, **33**, 13 (2001).

[15] D. E. Leyden and R. H. Cox, Analytical Applications of NMR, John Wiley & Sons, New York 1977, p. 185.

[16] M. Jesberger, T. P. Davis and L. Barner, *Synthesis*, 1929 (2003).

[17] B. S. Pedersen and S. O. Lawesson, *Tetrahedron*, **35**, 2433 (1979).

[18] A. A. El-Barbary and S. O. Lawesson, *Tetrahedron*, **37**, 2641 (1981).

[19] K. Kostka and M. Porada, *Arch. Pharm*., **325**, 325 (1992).

[20] K. Kostka, M. Porada, E. Zyner, W. Pakulska and A. Sadlowska, *Arch. Pharm*., **330**, 203 (1997).