A study of [1]benzofuro[3,2-*c*]pyridine derivatives

Denisa Tarabová,[a] Ján Titiš,[a] Naďa Prónayová,[b] Anton Gatial,[c] and Alžbeta Krutošíková[a]*

[a]*Department of Chemistry, Faculty of Natural Sciences, University of St. Cyril and Methodius, SK-917 01 Trnava, Slovakia*
[b]*Department of NMR and MS Spectroscopy, Faculty of Chemical and Food Technology, Slovak University of Technology, SK-812 37 Bratislava, Slovakia*
[c]*Institute of Physical Chemistry and Chemical Physics, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia*
E-mail: alzbeta.krutosikova@ucm.sk

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.925

Abstract

2-Methyl[1]benzofuro[3,2-*c*]pyridin-1-one **2** was obtained by reaction of the pyridone **1** with NaH followed by methylation with methyl iodide. The reaction of **1** with excess of P_4S_{10} rendered the corresponding thione **3,** which was methylated in PTC conditions giving 1-methylsulfanyl[1]benzofuro[3,2-*c*]pyridine **4**. The reactions of 1-chloro[1]benzofuro[3,2-*c*]pyridine **5** with excess of heterocyclic secondary amines (piperidine, morpholine and pyrrolidine) gave 1-substituted [1]benzofuro[3,2-*c*]pyridines **6-8**. Suzuki coupling reactions were realized with chloro-derivative **5** and phenylboronic or pyridine-3-boronic acids when 1-phenyl[1]benzofuro[3,2-*c*]pyridine **9** or 1-(pyridin-3-yl)[1]benzofuro[3,2-*c*]pyridine **10** were obtained. 2-Amino[1]benzofuro[3,2-*c*]pyridin-2-ium 4-methylbenzene sulfonate **12** was prepared by *N*-amination of [1]benzofuro[3,2-*c*]pyridine **11** with 1-[(aminooxy)sulfonyl]-4-methylbenzene. Then **12** was transformed into an unisolated zwitterionic *N*-imide **13**, which afforded by 1,3-dipolar cycloaddition reactions with dimethyl but-2-ynedioate (DMBD) or ethyl propiolate the corresponding 1-benzofuro[3,2-*c*]pyrazolo[1,5-*a*]pyridine carboxylic acid-esters **14, 15**. The reaction of **11** with benzoylnitromethane and DMBD gave benzoyl dimethyl ester **16**. The structures of all new compounds were proved by IR and ^{1}H and ^{13}C NMR spectra and the structure of 1-phenyl[1]benzofuro[3,2-*c*]pyridine was proved by X-ray analysis.

Keywords: Fused [1]benzofurans, pyridines, pyrazoles, pyrroles; nucleophilic substitution, coupling reactions, *N*-imines, 1,3-dipolar cycloaddition

Introduction

A variety of fused pyridines have been studied a for a long time in the field of the chemistry of heterocyclic compounds.[1,2] Furopyridines are very similar to such skeletons as quinoline and isoquinoline which are present in many compounds possessing biological activity. It was reported that some pharmacophores with potential antipsychotic activity contain the thieno- and furo-[3,2-*c*]pyridine ring systems.[3] By studying[4] of biological activity of tetrahydro-benzofuropyridines and benzothienopyridines was determined that these two groups are a part of compounds which show a high affinity in face of subtypes of receptors α_1 and α_2. This fact incites chemists about more complete explication of the structure and functions of these systems. Biological activity of the copper(II) and cobalt(II) 3-methylsufanylnicotinate complexes with furopyridines against various strains of bacteria and filamentous fungi has been investigated.[5,6]

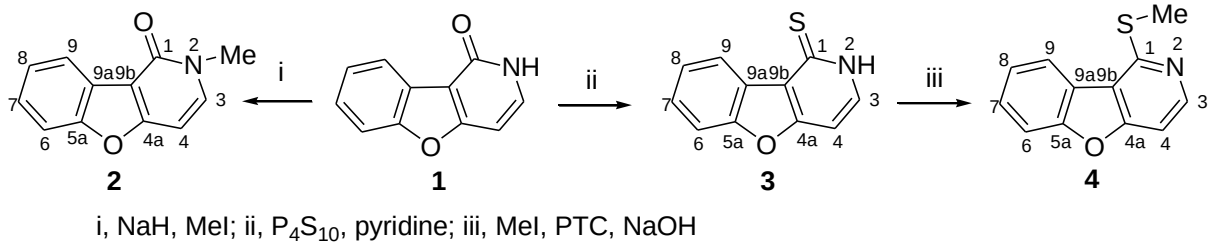
For a long time we have been interested in studying of the synthesis and reactivity of various furo[3,2-*c*]pyridines.[7-13] This type of the fused heterocycles can be readily coordinated to metal centers through *N*-donor atom. A few from these compounds were used as ligands in the preparation of coordination compounds with transition metals Cu(II) Co(II) and Ni(II). The spectral, magnetic, thermal properties, coordination chemistry and X-ray analysis of these compounds have already been outlined.[14-19]

Later on our attention was directed onto [1]benzofuro[3,2-*c*]pyridine system which is tricyclic heterosystem consisted from furopyridine ring fused with benzene ring.

Recently starting from [1]benzofuro[3,2-*c*]pyridine were successfully prepared the complex compounds and solved structures of tetra-μ-acetato-bis(1-benzofuro[3,2-*c*]pyridine-copper(II) and bis(1-benzofuro[3,2-*c*]pyridine-κN)dichlorocobalt(II).[20,21] We have published the synthesis and some reactions [1]benzofuro[3,2-*c*]pyridine and the study of the thermal stability of the mentioned complexes.[22] According our best knowledge until now there were not studied other reactions of [1]benzofuro[3,2-*c*]pyridine **11** or its intermediates **1, 5,** therefore we focused our attention on eliminating this shortcoming and herein we present our achieved results.

Results and Discussion

The synthesis of [1]benzofuro[3,2-*c*]pyridin-1(2*H*)-one **1** was already described.[22] 2-Methyl[1]benzofuro[3,2-*c*]pyridin-1-one **2** was obtained by reaction of **1** with NaH and then methylated with methyl iodide. The reaction of **1** with the excess of P_4S_{10} rendered the corresponding thione **3,** which was methylated in PTC conditions giving 1-methylsulfanyl[1]benzofuro[3,2-*c*]pyridine **4** (Scheme 1). Replacement of oxygen of C=O group with a sulfur atom in the compound **1**[22] is associated with a downfield shift of the pyridine proton signals. The vibrational wavenumbers of NH and C=N bonds in **3** lay within the range of 3 210- 3 250 cm^{-1} and 1 538-1591 cm^{-1}, respectively. The chemical shifts of pyridine ring protons (H-3 H-4) were also shifted downfield by aromatization **3** into **4**.



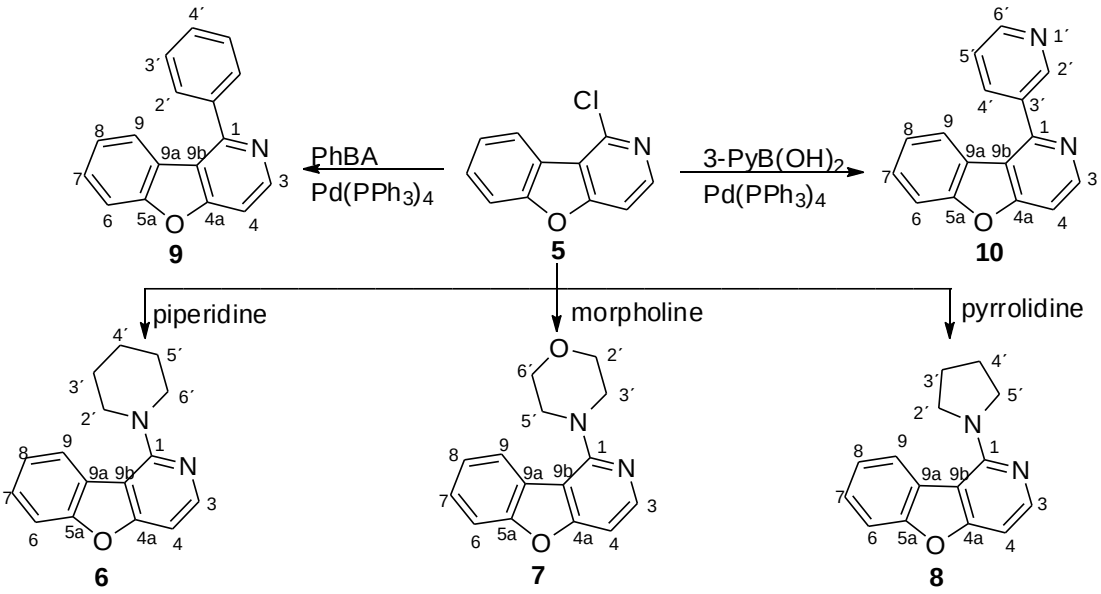
Scheme 1. Reactions of [1]benzofuro[3,2-*c*]pyridin-1(2*H*)-one.

1-Chloro[1]benzofuro[3,2-*c*]pyridine **5** was synthesized by a four step method starting from 1-benzofuran-2-carbaldehyde as described in ref. 22. Refluxing of **5** with heterocyclic secondary amines (piperidine, morpholine and pyrrolidine) gave **6-8** in moderate yields. The compound **6** was purified on a silica gel column. Suzuki coupling reaction was realized with **5** and phenylboronic acid or pyridin-3-ylboronic acid in the presence of $Pd(PPh_3)_4$ catalyst in dichloromethane 1-phenyl[1]benzofuro[3,2-*c*]pyridine **9** and 1-(pyridin-3-yl)[1]benzofuro[3,2-*c*]pyridine **10** were formed (Scheme 2). The structure of **9** was determined by X-ray analysis (Fig. 1 and Fig. 2), as well by ^{1}H and ^{13}C NMR spectra. ^{13}C NMR spectrum shows that the replacement of chlorine in the compound **5** C-1 (147.1 ppm[22]) with phenyl ring is associated with a downfield shift of C-1 carbon signal of the compound **9** (154.6 ppm).

The compounds **9** and **10** were used as *N*-ligands in the preparation of coordination compounds with transition metals Co(II) and Ni(II). Unfortunately all experiments which were done with **9** so far were unsuccessful; we supposed that it could be explained by a steric hindrance of the substituent attached at the C1 position. The structure of 1-phenyl[1]benzofuro[3,2-*c*]pyridine **9** was proved by X-ray analysis, then explained the reason of our coordination experiment failures.

The crystal data collection and the refinement results 1-phenyl[1]benzofuro[3,2-*c*]pyridine **9** are given in Table 1.

1-Phenyl[1]benzofuro[3,2-*c*]pyridine **9** crystallizes in $P2_12_12_1$ space group with unit cell containing 8 molecules of **9**. The crystal structure is composed of a two types of conformational isomers of 1-phenyl[1]benzofuro[3,2-*c*]pyridine. It has been found that the planes of the phenyl rings are turned in a way so that their dihedral angles with the C^{bzfupy}–C^{ph} vector are: ↑N-C9-C14-C = –136° and ↑N-C28-C33-C = +133°, respectively. This fact suggests the possibility of a partial rotation of the phenyl ring around the C^{bzfupy}–C^{ph} bond in solution. Therefore, the concomitant stereo shielding of the nitrogen atom may explain the weak coordination activity of the 1-phenyl[1]benzofuro[3,2-*c*]pyridine molecule.



Scheme 2. The nucleophilic and coupling reactions of 1-chloro[1]benzofuro[3,2-*c*]pyridine.

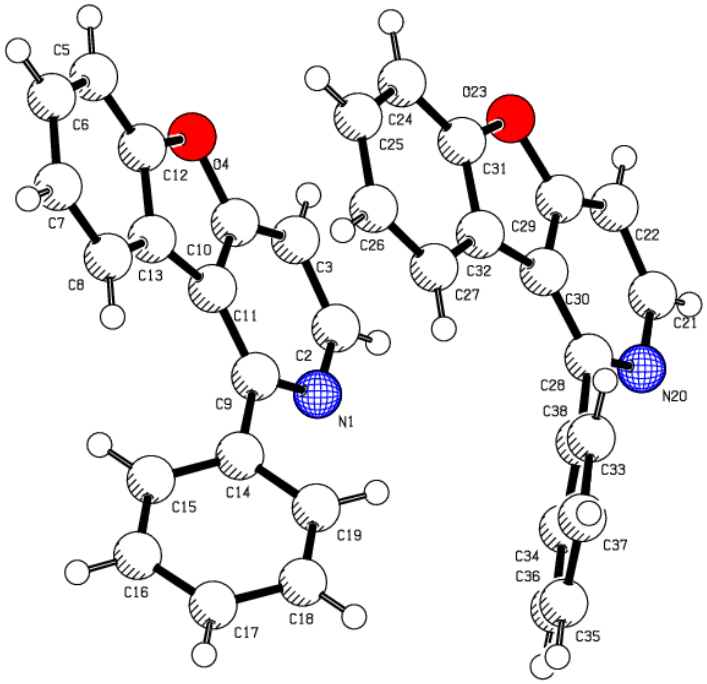


Figure 1. The molecular X-ray structure of 1-phenyl[1]benzofuro[3,2-*c*]pyridine **9**.

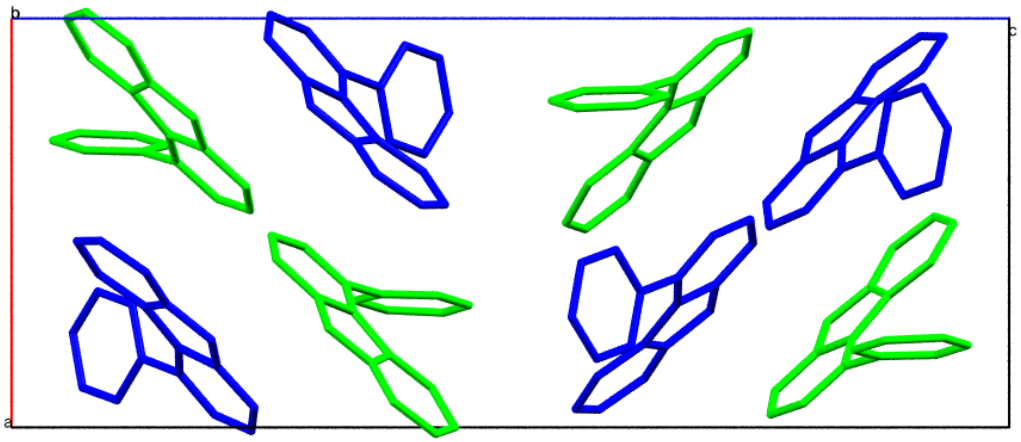


Figure 2. Crystal packing of 1-phenyl[1]benzofuro[3,2-*c*]pyridine **9**.
Notes: (i) view along the crystallographic *b* axis; (ii) the individual molecules are colored by symmetry equivalence.

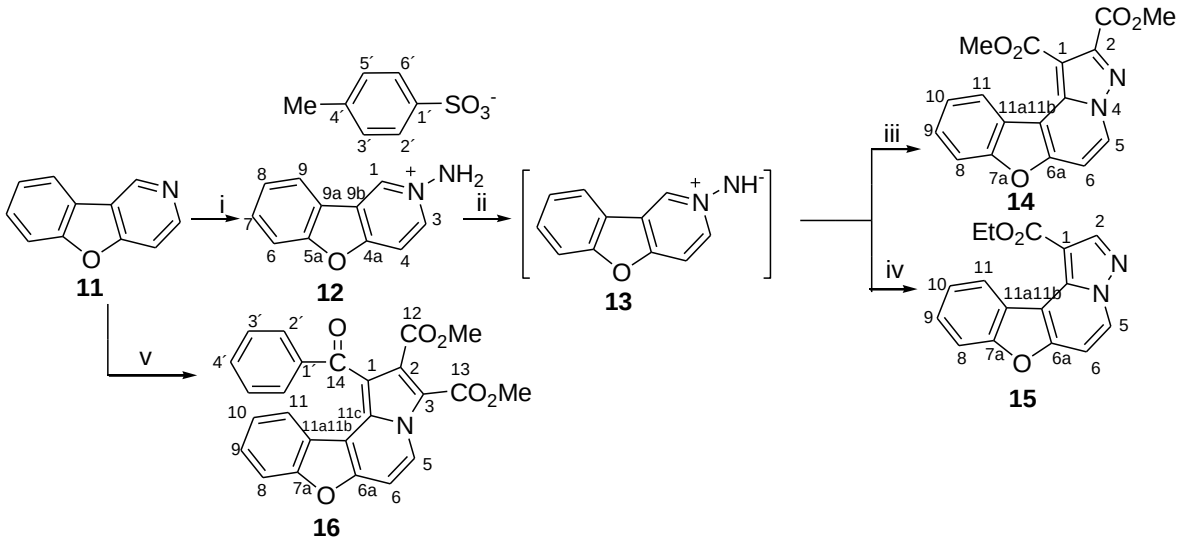
Table 1. Crystal data and the structure refinement for 1-phenyl[1]benzofuro[3,2-*c*]pyridine **9**

Crystallographic system	Orthorhombic
Space group	$P2_12_12_1$
a /Å	9.8818
b /Å	10.4110
c /Å	24.0356
α /°	90
β /°	90
γ /°	90
Volume /Å^3	2472.8
Z	8
D_{calc} /g cm^{-3}	1.318
Abs. coeficient μ /mm^{-1}	0.651
F(000)	1024
Temperature /K	293
Reflections collected	3561
Refinement method	Full matrix, least-squares on F^2
Data/Restrains/Parameters	3561/0/344
Goodness-of-fit on F^2	0.735
Final *R* indices ($I > 2\sigma(I)$)	R_1 = 0.0362, wR_2 = 0.0632
CCDC deposit number	756373

On the other hand the compound **10** can be readily coordinated to metal centers through N-donor atom of the unfused pyridine ring. The preparation of coordination compounds of **10** with transition metals Co(II) and Ni(II) is in progress.

In the past one of us has been a co-author of the paper dealing of the synthesis pyrazole fused furopyridines.[23] At that time [1]benzofuro[3,2-*c*]pyridine **11** was omitted to be studied in these reactions leading to fused pyrazole ring onto **11**. For that reason we prepared 2-amino[1]benzofuro[3,2-*c*]pyridin-2-ium-4-methylbenzene sulfonate **12** by direct *N*-amination of **11** with 1-[(aminooxy)sulfonyl]-4-methylbenzene in dichloromethane. Compound **12** is a white crystalline solid soluble in water. We supposed that on treatment with potassium carbonate in *N*,*N*-dimethylformamide, **12** is transformed in situ to a non-isolable zwitterionic *N*-imid **13,** analogously, as it was described in pyridine series by Huisgen and coworkers.[24] Further reactions with dienophiles confirmed our assumption. We found that **13** affords the corresponding 1-benzofuro[3,2-*c*]pyrazolo[1,5-*a*]pyridine carboxylic acid-esters **14** and **15** by 1,3-dipolar cycloaddition reactions with dimethyl but-2-ynedioate (DMBD) or ethyl propiolate. As shown by ^{1}H NMR spectra of crude products, the reaction gives, under given conditions, only compounds **14** or **15** without any side products of the bituminous unidentified material. The yields of **14** and **15** were unfortunately low, but they are comparable with were observed in the furo[3,2-*c*]pyridine series.[23] The ^{1}H NMR spectrum of **12** shows a doublet of H-4 with the coupling constant $^3J_{(4,3)}$ = 7.2 Hz. Protons of NH_2 are shown as a broad signal at δ = 8.3 ppm. Signals of the protons H-1 and H-3 are shifted to higher values compared to the starting compound **11** ref**.** 22 due to presence of a positively charged nitrogen atom of pyridine part of [1]benzofuro[3,2-*c*]pyridine system. The structure elucidation of 1,3-dipolar cycloadducts **14** and **15** was accomplished by NMR spectra. The transformation was verified by disappearance of the most downfield signal H-1 of the starting compound **12** and the appearance of alkyl proton signals of ester groups. Formation of a pyrazole ring containing **15** was supported by appearance of H-2 proton signal. 2D-spectra (gCOSY, gHSQCAD and gHMBCAD) were used for assignment of carbon signals in the synthesized compounds.

The reaction of **11** with benzoylnitromethane and DMBD gave benzoyl dimethyl ester **16**. The preparation of **16** was stimulated by an interesting publication[25] in which the authors described a simple synthesis of functionalized pyrrolo[2,1-*a*]isoquinolines and other important derivatives. The reaction forming fused pyrroles is related to the cycloadditions of quinolinium and isoquinolinium ylides with electron-deficient acetylenes.[25] It was interesting for us to compare the behavior our system **11** with isoquinoline in analogous reaction conditions. Firstly we repeated the reaction with isoquinoline according procedure which was published in ref. 25. We obtained the same results as the authors[25] published. However, we have been not able to get the better yield starting from **11** without any side products of the bituminous unidentified material. According us, it can be explained, that our compound **11**, possessing in its structure installed of the electron rich furan ring between benzene and pyridine rings, is less reactive than isoquinoline one.



i, 1-[(aminooxy)sufonyl]-4-methylbenzene; ii, K_2CO_3, DMF; iii, DMBD; iv, ethyl propionate; v, benzoylnitromethane, DMBD.

Scheme 3. Cyclization reactions on [1]benzofuro[3,2-*c*]pyridine **11**.

Conclusions

In summary we developed the synthesis of 1-substituted [1]benzofuro[3,2-*c*]pyridines from 1-chloro[1]benzofuro[3,2-*c*]pyridine by nucleophilic substitutions or Suzuki coupling reaction. In addition it was performed the efficient preparation of new derivatives of [1]benzofuro[3,2-*c*]pyridines by 1,3-dipolar cycloaddition and addition reaction using dienophiles as are dimethyl but-2-ynedionate, ethyl propiolate.

Experimental Section

General. Melting points were determined using Kofler hot plate. All solvents were distilled and dried before use. All reagents were commercially available were used without purification. Elemental analyses were determined using an EAGER 300. IR spectra were taken on a FTIR Nicolet NEXUS 470 spectrophotometer using KBr pellets (0.5 mg in 300 mg KBr) in region 4000 – 400 cm^{-1}. For interpretation of IR spectra following abbreviations are used s = strong band (a value of transmittance: 0-35%), m = medium band (a value of transmittance: 36-50%) w = weak (a value of transmittance: over 50%). ^{1}H NMR spectra were measured in DMSO-d_6 using spectrometer Varian INOVA 600 (for ^{1}H 599,782 MHz and for ^{13}C 150.830 MHz) at 25 °C. Chemical shifts (δ-scale) are quoted in parts per million and following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet; coupling constants (J) are given in Hz.

X-Ray analysis was realized on apparatus Oxford X-calibur on CCD camera. The crystal structure of **9** was solved with SHELXS-97 using direct methods, while further refinement with full-matrix least squares on F^2 were carried out with SHELXL-97. All hydrogen atoms in the structure were found from difference Fourier map of electron density and refined independently of atoms to which they were bound. Geometrical analysis was performed using SHELXL- 97.

2-Methyl[1]benzofuro[3,2-*c*]pyridin-1-one (2). Pyridone **1** (1.85 g, 10 mmol) was suspended in dry dimethylformamide (10 mL) and NaH (60% in mineral oil; 0.54 g, 13 mgat) was added under stirring. When the evolution of hydrogen was complete, methyl iodide (2 g, 14 mmol) was added dropwise and the mixture stirred for 30 min. Then crushed ice was added and the mixture was extracted with chloroform. The organic layer was dried and evaporated in vacuum. The residue was triturated with diethyl ether and solid was collected by filtration. The crude product was crystallized from toluene. Yield 1.61 g, 80.9%, m.p. 123-125 °C; R_F = 0.75 (ethyl acetate). Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.32; H, 4.58; N, 7.03%. ^{1}H NMR (DMSO-d_6), δ: 8.02 (d, 1H, $^3J_{(9,8)}$ = 7.4 Hz, H-9), 7.87 (d, 1H, $^3J_{(6,7)}$ = 7.8 Hz, H-6), 7.66 (d, 1H, $^3J_{(3,4)}$ = 7.3 Hz, H-3); 7.42 (t, 1H, H-8), 7.40 (t, 1H, H-7), 6.78 (d, 1H, H-4), 3.57 (CH_3). ^{13}C NMR (DMSO-d_6), δ: 161.5 (C-1), 158.6 (C-4a), 154.3 (C-5a), 139.5 (C-3), 125.7(C-7), 124.1 (C-8), 123.6 (C-9a), 120.7 (C-9), 111.3 (C-6), 109.3 (C-9b), 94.2 (C-4), 36.1 (CH_3).

[1]Benzofuro[3,2-*c*]pyridine-1(2*H*)-thione (3). A mixture of pyridone **1** (1.85 g, 10 mmol) and phosphorus pentasulfide (2.22 g 10 mmol) in dry pyridine (20 mL) was refluxed for 5 h. The hot reaction mixture was poured into hot water (150 mL). The mixture was allowed to settle overnight. The precipitate was collected by filtration, washed with water and crystallized from aqueous ethanol (80%) giving pale yellow crystals of **3**. Yield 1.45 g, 72%, m.p. 255-258 °C; R_F = 0.55 (ethyl acetate). Anal. Calcd. for $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96; S, 15.93. Found: C, 65.78; H, 3.58; N, 7.03; S, 15.61%. ^{1}H NMR (DMSO-d_6), δ: 13.50 (s, 1H, NH), 8.77 (d, 1H, $^3J_{(9,8)}$ = 7.8 Hz, H-9), 7.86 (d, 1H, $^3J_{(3,4)}$ = 6.9 Hz, H-3), 7.74 (d, 1H, $^3J_{(6,7)}$ = 8.2 Hz, H-6), 7.54 (t, 1H, H-7), 7.48 (t, 1H, H-8), 7.28 (d, 1H, H-4). ^{13}C NMR (DMSO-d_6), δ: 173.9 (C-1), 159.1 (C-4a), 154.9 (C-5a), 137.6 (C-3), 127.3 (C-7), 124.1 (C-8), 123.8 (C-9a), 122.3 (C-9), 121.8 (C-9b), 111.2 (C-6), 100.1 (C-4).

1-Methylsulfanyl[1]benzofuro[3,2-*c*]pyridine (4). Thione **3** (1 g, 5 mmol) was suspended in dichloromethane (25 mL) under vigorous stirring tetrabutylammonium bromide (0.25 g, 0.75 mmol) was added, followed by a solution of NaOH (1 g, 25 mmol) in water (2.5 mL). The mixture was stirred for 15 min; then methyl iodide (1.4 g, 10 mmol) was added dropwise. The stirring was continued for 20 min, the organic layer was separated, washed with water, dried with Na_2SO_4, evaporated *in vacuo* and crystallized from methanol giving **4** as white crystals. Yield 0.61g, 56.7%, m.p. 238 °C. R_F = 0.62 (ethyl acetate)**.** Anal. Calcd. for $C_{12}H_9NOS$: C, 66.95; H, 4.21; N, 6.51; S, 14.09. Found: C, 67.08; H, 4.26; N, 6.53; S, 13.80%. ^{1}H NMR (DMSO-d_6), δ: 8.52 (d, 1H, $^3J_{(3,4)}$ = 5.7 Hz, H-3), 8.07 (d, 1H, $^3J_{(9,8)}$ = 7.5 Hz, H-9), 7.78 (d, 1H, $^3J_{(6,7)}$ = 8.3 Hz, H-6), 7.60 (t, 1H, H-7), 7.54 (d, 1H, H-4), 7.52 (t, 1H, H-8), 2.73 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6), δ: 159.8

(C-4a), 154.7 (C-5a), 154.0 (C-1), 147.1 (C-3), 128.0 (C-7), 124.2 C-8), 122.3 (C-9), 120.8 (C-9a), 117.1(C-9b), 111.8 (C-6), 104.0 (C-4), 11.9 (CH_3).

1-(Piperidin-1-yl)[1]benzofuro[3,2-*c*]pyridine (6). 1-Chloro[1]benzofuro[3,2-*c*]pyridine (**5**) (1.63 g, 8 mmol) was refluxed in piperidine (7.4 mL) for 48 h. The excess of the amine was distilled off under reduced pressure and the residue was purified on a silica gel column (25 g) eluting with chloroform. The product was crystallized from hexane. Yield 0.81 g, 40%, m.p. 78-80 °C; R_F = 0.62 (ethyl acetate). Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.95; H, 6.51; N, 11.16%. ^{1}H NMR (DMSO-d_6), δ: 8.24 (d, 1H, $^3J_{(3,4)}$ = 5.7 Hz, H-3). 7.75 (d, 1H, $^3J_{(9,8)}$ = 7.6 Hz, H-9), 7.72 (d, 1H, $^3J_{(6,7)}$ = 7.9 Hz, H-6), 7.52 (t, 1H, H-7), 7.48 (t, 1H, H-8), 7.27 (d, 1H, H-4), 3.27 (bs, 4H, H-2´, H-6´), 1.74 (m, 4H, H-3´, H-5´), 1.63 (m, 2H, H-4´). ^{13}C NMR (DMSO-d_6), δ: 162.2 (C-1), 158.2 (C-4a), 154.3 (C-5a), 145.7 (C-3), 126.8 (C-7), 123.9 (C-8), 122.1 (C-9), 121.3 (C-9a, 111.4 (C-6), 109.1 (C-9b), 101.6 (C-4), 49.8 (C-2´, C-6´), 25.5 (C-3´, C-5´), 24.0 (C-4´). IR spectrum, ν/cm^{-1}: 2986m, 2951m, 2936s, 2929s, 2919s, 2849m, 2825m, 1620w, 1589s, 1565s, 1469m, 1434s, 1375s, 1281s, 1247s, 1211s, 1192m, 1117m, 1083s, 1002s, 811m, 791w, 785w, 749s, 738m, 696w.

1-(Morpholin-4-yl)[1]benzofuro[3,2-*c*]pyridine (7). The compound **7** was prepared according to the above procedure. Yield 49%, m.p. 71-73 °C (hexane); R_F = 0.71 (ethyl acetate)
Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.71; H, 5.35; N, 10.92%.
^{1}H NMR (DMSO-d_6), δ: 8.27 (d, 1H, $^3J_{(3,4)}$ = 5.7 Hz, H-3), 7.75 (d, 1H, $^3J_{(9,8)}$ = 8.0 Hz, H-9), 7.73 (d, 1H, $^3J_{(6,7)}$ = 8.3 Hz, H-6), 7.53 (t, 1H, H-7), 7.48 (t, 1H, H-8), 7.33 (d, 1H, H-4), 3.86 (t, 4H, H-2´ H-6´), 3.35 (t, 4H, H-3´, H-5´). ^{13}C NMR (DMSO-d_6), δ: 162.3 (C-1), 157.5 (C-4a), 154.5 (C-5a), 145.7 (C-3), 127.1 (C-7), 124.0 (C-8), 122.4 (C-9), 120.7 (C-9a), 111.5 (C-6), 109.4 (C-9b), 102.3 (C-4), 66.1 (C-2´, C-6´), 49.2 (C-3´, C-5´). IR spectrum, ν/cm^{-1}: 3058s, 3036s, 2994s, 2976s, 1646m, 1589s, 1575s, 1467s, 1444s, 1434s, 1372s, 1366s, 1333s, 1294m, 1277s, 1269s, 1244s, 1234s, 1191s, 1170m, 1113s, 1097s, 1070s, 1030s, 1019s, 894s, 846s, 823s, 796m, 750s, 736s, 666m, 659m, 535m.

1-(Pyrrolidin-1-yl)[1]benzofuro[3,2-*c*]pyridine (8). The compound **8** was prepared according to the above procedure. Yield 52%, m.p. 80-83 °C (hexane); R_F = 0.54 (ethyl acetate)
Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.71; H, 5.90; N, 11.82%
^{1}H NMR (DMSO-d_6), δ: 8.12 (d, 1H, $^3J_{(3,4)}$ = 5.6 Hz, H-3), 8.01 (d, 1H, $^3J_{(9,8)}$ = 7.6 Hz, H-9), 7.66 (d, 1H, $^3J_{(6,7)}$ = 8.2 Hz, H-6), 7.44 (t, 1H, H-7), 7.37(t, 1H, H-8), 7.03 (d, 1H, H-4), 3.72 (d, 4H, H-2´, H-5´), 1.91 (d, 4H, H-3´, H-4´). ^{13}C NMR (DMSO-d_6), δ: 162.6 (C-1), 154.8 (C-4a), 154.2 (C-5a), 145.3 (C-3), 125.8 (C-8), 123.5 (C-7), 122.7 (C-9), 121.9 (C-9a), 111.2 (C-6), 105.4 (C-9b), 99.3 (C-4), 49.6 (C-2´, C-5´), 25.1 (C-3´, C-4´). IR spectrum, ν/cm^{-1}: 2966s, 2866s, 1934w, 1768w, 1618m, 1589s, 1560s, 1444s, 1419s, 1370m, 1342m, 1323m, 1296s, 1289s, 1268m, 1249w, 1225s, 1192m, 1111s, 1093s, 1032m, 1021w, 990w, 905w, 790s, 746s, 736s, 658m, 531w.

1-Phenyl[1]benzofuro[3,2-*c*]pyridine (9). The mixture of 1-chloro[1]benzofuro[3,2-*c*]pyridine (**5**) (1.018 g; 5 mmol), phenyl boronic acid (0.945 g; 8 mmol), water solution of sodium carbonate (2 M, 7.5 mL) and $Pd(PPh_3)_4$ (0.345 g, 0.3 mmol) in 1,2-dimethoxyethane (7.5 mL)

was heated at 80 °C for 6 h. Then the reaction mixture was poured into mixture dichloromethane and ice water (1:1). The separate organic layer was washed with water and brine, dried with magnesium sulfate, the solvent was evaporated in vacuum and residue was crystallized in methanol. Yield of **9** 59%, m.p. 125 °C; R_F = 0.42 (ethyl acetate).Anal. Calcd. for $C_{17}H_{11}NO$: C, 83.25; H, 4.52; N, 5.71. Found: C, 83.04; H, 4.50; N, 5.46%. ^{1}H NMR (DMSO-d_6), δ: 8.70 (d, 1H, $^3J_{(3,4)}$ = 5.4 Hz, H-3), 7.81 (d, 2H, ^3J = 7.8 Hz, H-3´, H-5´), 7.77 (d, 1H, $^3J_{(6,7)}$ = 7.8 Hz, H-6), 7.75 (d, 1H, H-4), 7.65 (d, 1H, $^3J_{(9,8)}$ = 7.8 Hz, H-9), 7.60 (2H, ^3J = 6.6 Hz, H-2´, H-6´), 7.55 (t, 1H, H-7), 7.54 (t, 1H, H-4´), 7.32 (t, 1H, H-8).^{13}C NMR (DMSO-d_6), δ: 161.2 (C-4a), 155.2 (C-5a), 154.6 (C-1), 147.3 (C-3), 138.9 (C-1´), 129.3 (C-4´), 128.6 (C-2´, C-6´), 128.6 (C-7), 128.5 (C-3´, C-5´), 123.7 (C-8), 121.9 (C-9), 120.9 (C-9a), 117.8 (C-9b), 112.0 (C-6), 106.3 (C-4). IR spectrum, ν/cm^{-1}: 3053s, 3030m, 2971m, 2923m, 1649m, 1629m, 1586s, 1497s, 1414s, 1337s, 1318m, 1291s, 1252m, 1225s, 1191s, 1120s, 1082m, 1070s, 1024m, 998s, 979m, 959w, 925s, 852s, 849s, 798s, 765s, 661m, 652s, 544m, 443m, 430w.

1-(Pyridin-3-yl)[1]benzofuro[3,2-*c*]pyridine (10). The mixture of 1-chloro[1]benzofuro[3,2-*c*]pyridine (**5**) (0.78 g; 3.8 mmol), pyridine-3-boronic acid (0.86 g; 7 mmol), water solution of sodium carbonate (2 M, 4.5 mL) and $Pd(PPh_3)_4$ (258 mg, 0.23 mmol) in dimethoxyethane (6.7 mL) was heated at 80 °C for 5 h. Then the reaction mixture was poured into mixture dichloromethane and ice water (1:1). The separate organic layer was washed with aqueous solution sodium carbonate (5%) and brine, dried with magnesium sulfate. The solvents were evaporated in vacuum and residue was crystallized in methanol. The product **10** is white crystalline solid. Yield: 0.51 g (54.5%) m.p. 89-90 °C.Anal. Calcd. for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09; N, 11.38. Found: C, 78.31; H, 4.33; N, 11.26%. ^{1}H NMR (DMSO-d_6), δ: 9.02 (s, 1H, H-2´), 8.80 (d,d, 1H, $^3J_{(6´,5´)}$ = 4.8 Hz, $^4J_{(6´,4´)}$ = 1.2 Hz, H-6´), 8.76 (d, 1H, $^3J_{(3,4)}$ = 5.4 Hz, H-3), 8.26 (d,d, 1H, $^3J_{(4´,5´)}$ = 6.0 Hz, $^4J_{(4´,6´)}$ = 1.2 Hz, H-4´), 7.84 (d, 1H, H-4), 7.82 (d, 1H, $^3J_{(6,7)}$ = 7.8 Hz, H-6), 7.66 (dd, 1H, $^3J_{(5´,6´)}$ = 4.8 Hz, $^3J_{(5´,4´)}$ = 6.0 Hz, H-5´), 7.61 (d, 1H, $^3J_{(9,8)}$ = 7.8 Hz, H-9), 7.54 (t, 1H, H-7), 7.37 (t, 1H, H-8). ^{13}C NMR (DMSO-d_6), δ: 161.2 (C-4a), 155.3 (C-5a), 151.6 (C-1), 150.2 (C-6´), 149.2 (C-2´), 147.6 (C-3), 136.2 (C-4´), 134.6 (C-1´), 128.9 (C-7), 124.0 (C-8), 123.7 (C-5´), 121.6 (C-9), 120.6 (C-9a), 118.3 (C-9b), 112.2 (C-6), 106.9 (C-4).
IR spectrum, ν/cm^{-1}: 3121m, 1968m, 1657m, 1588s, 1577s, 1561s, 1477s, 1463m, 1422s, 1330m, 1311w, 1294s, 1225m, 1184s, 1028m, 961w, 935s, 847s, 788m, 748s, 705m, 661s, 654m, 574w, 543s, 501w, 457m, 419w.

2-Amino[1]benzofuro[3,2-*c*]pyridin-2-ium 4-methylbenzene sulfonate (12). A solution of 1-[(aminooxy)sufonyl]-4-methylbenzene (1 g, 5.3 mmol) in dichloromethane (2 mL) was added to a stirred solution of **11** (0.597 g, 3.5 mmol) in dichloromethane (1.5 mL) at room temperature. Stirring was continued for 5 h. The product was then precipitated by the addition of diethyl ether (20 mL), filtered off and crystallized from methanol to yield 1.12 g, 89.9%, m.p. 135 °C. Anal. Calcd. for $C_{18}H_{16}N_2O_4S$: C, 60.66; H, 4.53; N, 7.86; S, 9.00. Found: C, 60.32; H, 4.56; N, 7.52; S, 8.85%. ^{1}H NMR (DMSO-d_6), δ: 9.86 (s, 1H, H-1), 8.92 (d, 1H, $^3J_{(3,4)}$ = 7.2 Hz, H-3), 8.40 (d, 1H, $^3J_{(4,3)}$ = 7.2 Hz, H-4), 8.38 (d, 1H, $^3J_{(8,9)}$ = 7.8 Hz, H-9), 8.30 (brs, 2H, NH_2), 7.96 (d, 1H, $^3J_{(6,7)}$ = 9.0 Hz, H-6), 7.80 (t, 1H, H-7), 7.64 (t, 1H, H-8), 7.48 (d, 2H, $^3J_{(2´,3´)}$ = 8.4 Hz, H-2´, H-

6´), 7.07 (d, 1H, $^{3}J_{(5',6')}$ = 7.8 Hz, H-3´, H-5´), 2.24 (s, 3H, H-CH_3). ^{13}C NMR (DMSO-d_6), δ: 160.2 (C-3a), 157.2 (C-4a), 145.4 (C-2´), 140.1 (C-2), 137.7 (C-4´), 136.9 (C-9), 131.4 (C-6), 128.0 (C-3´), 125.5 (C-7), 125.4 (C-2´), 123.7 (C-8b), 123.2 (C-8), 119.4 (C-8a), 112.7 (C- 5), 111.0 (C-3), 20.7 (CH_3). IR (KBr) ν_{max}/cm^{-1}: 3141(m), 3117(m), 3085(m), 3058(m), 2925(w), 1718(w), 1612(w), 1599(w), 1527(w), 1484(w), 1461(s), 1453(m), 1418(w), 1382(w), 1272(w), 1209(s), 1187(s), 1153(m), 1123(s), 1108(w), 1034(s), 1010(s), 905(w), 843(m), 816(m), 774(m), 736(w), 684(s), 625(w), 586(w), 568(s).

Dimethyl 1-benzofuro[3,2-*c*]pyrazolo[1,5-*a*]pyridine-1,2-dicarboxylate (14). To a stirred solution of **12** (1.068 g, 3 mmol) in *N*,*N*-dimethylformamide (20 mL) was added potassium carbonate (0.49 g, 3.5 mmol) and dimethyl but-2-ynedioate (0.67 g, 4.7 mmol). The reaction mixture was intensively stirred for 24 h at room temperature. The solvent was evaporated under reduced pressure, the residue was dissolved in diethyl ether and the insoluble material was filtered off. The filtrate was concentrated under diminished pressure and the product was crystallized from diethyl ether to yield 0.325 g, 33.5%, m.p. 147 °C. Anal. Calcd. for $C_{17}H_{12}N_2O_5$: C, 57.42; H, 3.13; N, 6.70. Found: C, 57.55; H, 3.36; N, 6.58%. ^{1}H NMR (DMSO-d_6), δ: 8.94 (d, 1H, $^{3}J_{(5,6)}$ = 7.8 Hz, H-5), 8.08 (d, 1H, $^{3}J_{(11,10)}$ = 7.8 Hz, H-11);, 7.75 (d, 1H, $^{3}J_{(8,9)}$ = 8.4 Hz, H-8), 7.71 (d, 1H, H-6), 7.54 (t, 1H, H-9), 7.44 (t, 1H, H-10), 3.93 (s, 3H, 2-OCH_3), 3.88 (s, 3H, 1-OCH_3). ^{13}C NMR (DMSO-d_6), δ: 163.5 (C=O), 162.4 (C=O), 155.2 (C-7a), 153.5 (C-6a), 145.6 (C-2), 135.3 (C-11c), 130.2 (C-5), 127.3 (C-9), 124.0 (C-10), 123.3 (C-11), 121.5 (C-11a), 111.8 (C-8), 110.4 (C-11b), 104.2 (C-1), 103.8 (C-6), 52.7 (1-OMe), 52.4 (2-OMe). IR (KBr) ν_{max}/cm^{-1}: 3041(m), 2918(w), 1729(s), 1642(m), 1619(w), 1543(m), 1461(s), 1411(w), 1377(s), 1334(w), 1300(s), 1245(s), 1170(m), 1115(w), 1100(m), 1065(w), 1015(w), 962(w), 869(w), 795(s), 749(m), 681(w), 523(w).

Ethyl 1-benzofuro[3,2-*c*]pyrazolo[1,5-*a*]pyridine-1-carboxylate (15). This compound was prepared according to the previous procedure described for compound **14**. Yield: 0.286 g, 34.1%, m.p. 179 °C. Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 60.97; H, 3.50; N, 7.48. Found: C, 60.78; H, 3.51; N, 7.42%. ^{1}H NMR ($CDCl_3$), δ: 9.01 (d, 1H, $^{3}J_{(11,10)}$ = 7.8 Hz, H-11), 8.64 (d, 1H, $^{3}J_{(5,6)}$ = 7.2 Hz, H-5), 8.47 (s, 1H, H-2), 7.63 (d, 1H, $^{3}J_{(8,11)}$ = 7.8 Hz, H-8), 7.50 (t, 1H, H-9), 7.47 (t, 1H, H-10), 7.36 (d, 1H, $^{3}J_{(6,7)}$ = 7.2 Hz, H-6), 4.45 (q, 2H, OCH_2), 1.46 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 163.0 (CO), 155.9 (C-6a, C-7a), 146.3 (C-2), 136.54 (C-11b), 129.5 (C-5), 126.9 (C-9), 125.9 (C-11), 123.7, (C-10), 122.8 (C-11a), 112.0 (C-11b), 111.1 (C-8), 104.9 (C-1), 101.9 (C-6), 60.2 (CH_2), 14.5 (CH_3). IR (KBr) ν_{max}/cm^{-1}: 3053(s), 3030(m), 2852(w), 1819(w), 1628(w), 1586(s), 1523(s), 1497(s), 1414(s), 1336(s), 1291(s), 1252(m), 1191(s), 1150(s), 1083(m), 998(m), 979(m), 959(w), 925(s), 839(s), 797(s), 735(s), 661(m), 652(s), 573(w), 543(s), 489(m), 443(m), 430(s).

Dimethyl 1-benzoyl[1]benzofuro[2,3-*g*]indolizine-2,3-dicarboxylate (16). To a stirred solution of dimethyl but-2-ynedioate (0.43 g, 3 mmol) and benzoylnitromethane (0.5 g, 3 mmol) in H_2O/MeCN (5:3) (5 mL) was added **11** (0.51 g, 3 mmol) at room temperature. The reaction mixture was then stirred for 3 h (TLC monitoring). The precipitate was filtered and crystallized from methanol to give **16** in yield 0.36 g, 25.5%, m.p. 205 °C. Anal. Cal. for $C_{25}H_{17}NO_6$: C,

70.25; H, 4.01; N, 3.28; Found: C, 69.95; H, 3.77; N, 3.58%. ^{1}H NMR (DMSO-d_6), δ: 9.54 (d, 1H, $^{3}J_{(5,6)}$ = 7.8 Hz, H-5), 7.87 (d, 2H, $^{3}J_{(2',3')}$ = 7.2 Hz, H-2´,.H-6´), 7.76 (t, 1H , H-8), 7.74 (d, 1H, H-6), 7.67 (t, 1H, H-4´), 7.53 (d, 2H, $^{3}J_{(3',2')}$ = 7.2 Hz, H-3´, H-5´), 7.47 (t, 1H, H-9), 7.28 (d, 1H, $^{3}J_{(11,10)}$ = 7.8 Hz, H-11), 7.26 (t, 1H, H-10). ^{13}C NMR (DMSO-d_6), δ: 190.6 (C-14), 164.5 (C-12), 160.0 (C-13), 154.9 (C-7a), 153.0 (C-6a), 138.3 (C-1´), 133.4 (C-4´), 131.5 (C-3), 129.5 (C-2´, C-6´), 128.5 (C-3´, C-5´), 128.5 (C-11c), 127,8 (C-5), 127.0 (C-9), 124.2 (C-10), 123.6 (C-11), 121.4 (C-11a), 113.2 (C-1), 111.9 (C-11b), 111.6 (C-8), 110.8 (C-2), 103.9 (C-6), 52.0 (1-OMe), 52.1 (2-OMe). IR (KBr) ν_{max}/cm^{-1}: 3058(m), 1734(s), 1698(s), 1645(s), 1626(m), 1616(w), 1595(s), 1578(m), 1552(w), 1521(s), 1476(w), 1454(s), 1425(m), 1386(s), 1369(m), 1311(s), 1290(m), 1279(w), 1245(s), 1168 (s), 1155(m), 1097(s), 1061(m), 1029(s), 1024(m), 1005(s), 980(m), 943(s), 927(m), 849(s), 833(w), 819(m), 794(m), 743(s), 718(m), 687(s), 642(m), 619(w).

Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 756373 for compound 1-phenyl[1]benzofuro[3,2-*c*]pyridine **9**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk; http://www.ccdc.ac.uk).

Acknowledgements

This work was supported by the grants VEGA 1/1005/09, APVV-0006-07 and VVCE-0004-07. NMR experimental part of this work was facilitated by support of Slovak National Research and Development Program No. 2003SP200280203. The authors are grateful to Prof. J. Kožíšek for X-ray analysis data.

References

1. Sherman, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. Eds.; Pergamon: Oxford, 1996; Vol. 7, pp 167-227.
2. Sherman, A. R. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. Eds.; Elsevier: Oxford, 2008; Vol. 10, pp 263-338.
3. New, J. S.; Christopher, W. L.; Yevich, J. P.; Butter, R.; Schlemmer Jr., R. S.; Van der Maelen, C. P.; Cipolline, J. A. *J. Med. Chem.* **1989**, *32*, 1147.

4. Kennis, L. E.; Bischoff, F. P.; Mertens, C. J.; Love, J. C.; Van Den Keybus, F. A.; Pieters, S.; Braeken, M.; Megens, A. A.; Leysen, J. E. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 71.
5. Segl'a, P.; Miklovič, J.; Mikloš, D.; Titiš, J.; Herchel, R.; Moncol, J.; Maliníková, B.; Hudecová, D.; Mrázová, V.; Lis, T.; Melník, M. *Transition Met. Chem.* **2008**, *33*, 967.
6. Segl'a, P.; Miklovič, J.; Mikloš, D.; Mrázová, V.; Krupková, L.; Hudecová, D.; Ondrušová, Z.; Švorec, J.; Moncol, J.; Melník, M. *Transition Met. Chem.* **2009**, *34*, 15.
7. Bobošík, V.; Krutošíková, A.; Jordis, U. *Monatsh. Chem.* 1**995**, *126*, 747.
8. Krutošíková, A.; Sleziak, R. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1627.
9. Gajdoš, P.; Miklovič, J.; Krutošíková, A. *Khim. Geterotsikl. Soed.* **2006**, *6*, 825.
10. Mojumdar, S. C.; Miklovič, J.; Krutošíková, A.; Valigura, D.; Steward, J. M. *J. Therm. Anal. Cal.* **2005**, *81*, 211.
11. Búdová, M.; Fojtíková, K.; Miklovič, J.; Mrázová, V.; Horváth, B.; Krutošíková, A. *Chem. Pap.* **2006**, *60*, 231.
12. Bradiaková, I.; Prónayová, N.; Gatial, A.; Krutošíková, A. *Chem. Pap.* **2008**, *62*, 428.
13. Bradiaková, I.; Ďurčeková, T.; Prónayová, N.; Gatial, A.; Krutošíková, A. *Chem. Pap.* **2009**, *63*, 586.
14. Krutošíková, A.; Mitasová, B.; Jóna, E.; Bobošíková, M. *Chem. Pap*. **2001**, *55*, 290.
15. Miklovič, J.; Krutošíková, A.; Baran, P. *Acta. Cryst.* **2004**, *Sec. C, 60*, m227.
16. Baran, P.; Boča, M.; Boča, R.; Krutošíková, A.; Miklovič, J.; Pelikán, J.; Titiš, J. *Polyhedron* **2005**, *24*, 1510.
17. Titiš, J.; Boča, R.; Dlháň, L.; Ďurčeková, T.; Fuess, H.; Ivaníková, R.; Mrázová, V.; Papánková, B.; Svoboda, I. *Polyhedron* **2007**, *26*, 1523.
18. Vrábel, V.; Švorc, Ľ.; Bradiaková, I.; Kožíšek, J.; Krutošíková, A. *Acta. Cryst.* **2007**, *E63*, o4516.
19. Boča, R.; Titiš, J. In *Coordination Chemistry Research Progress*; Cartere, T. W.; Verley K. S. Eds.; Nova Science Publishers, Inc.: New York 2008; pp 247–304.
20. Vrábel, V.; Švorc, Ľ.; Juristová, N.; Miklovič, J.; Kožíšek, J. *Acta. Cryst.* **2007**, *E63*, m2112.
21. Vrábel, V.; Švorc, Ľ.; Juristová, N.; Miklovič, J.; Kožíšek, J. *Acta. Cryst.* **2007**, *E63*, m2427.
22. Mojumdar, S. C.; Šimon, P.; Krutošíková, A. *J. Therm. Anal. Cal*. **2009**, *96*, 103.
23. Bencková, M.; Krutošíková, A. *Collect. Czech. Chem. Commun.* **1999**, *64*, 539.
24. Krischke, R.; Grashey, R.; Huisgen, R. *Liebigs Ann. Chem*. **1977**, 489.
25. Yavari, I.; Piltan, M.; Moradi, L. *Tetrahedron* **2009**, *65*, 2067**.**