

**TRANSFORMATIONS OF METHYL 2-BENZOYLAMINO-2-OXOBUTANOATE. THE SYNTHESIS OF OXAZOLO[4,5-*c*]QUINOLINE AND 1-SUBSTITUTED 1*H*-IMIDAZOLE-4-CARBOXYLATE DERIVATIVES**

**Urška Bratušek, Simon Rečnik, Jurij Svete\*, Anton Meden, and Branko Stanovnik\***

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia, e-mail: Branko.Stanovnik@uni-lj.si

**Abstract** – Methyl 2-benzoylamino-2-oxobutanoate (**1**) was transformed with aromatic amines (**2a–d**) into methyl 2-arylamino-2-(benzoylamino)but-2-enoates (**3a–d**). Cyclization of compounds (**3a–c**) in polyphosphoric acid affords a mixture of oxazolo[4,5-*c*]quinoline derivatives (**4a–c**) and 1-aryl-2-phenyl-5-methyl-1*H*-imidazole-4-carboxylates (**5a–c**), while compound **3d** gives a mixture of 9-bromo- (**4d**) and 7-bromooxazolo[4,5-*c*]quinoline derivative (**4d'**)

## INTRODUCTION

In the literature only limited number of syntheses of oxazolo[4,5-*c*]quinolines are described. They are obtained from 3-amino-4-hydroxyquinolines,<sup>1</sup> from isatoic anhydrides with  $\alpha$ -isocyanoacetates,<sup>2</sup> by Beckmann rearrangement of 3-acyl-4-hydroxy-2-quinolone oximes,<sup>3</sup> and from 4-azido-2(1*H*)-quinolones by thermolysis in the presence of carboxylic acids and polyphosphoric acid.<sup>4</sup> Many oxazoloquinoline derivatives have been found in the last decades to show antihypertensive and dopaminergic properties<sup>5</sup> and antiulcer,<sup>6</sup> anticancer,<sup>7</sup> antiallergic,<sup>8</sup> antidepressive,<sup>9</sup> or herbicidal activity.<sup>10</sup> Recently, immunomodulating effects of quinolines containing a carbamoyl group have been described<sup>11</sup> and for inducing cytokine biosynthesis.<sup>12</sup>

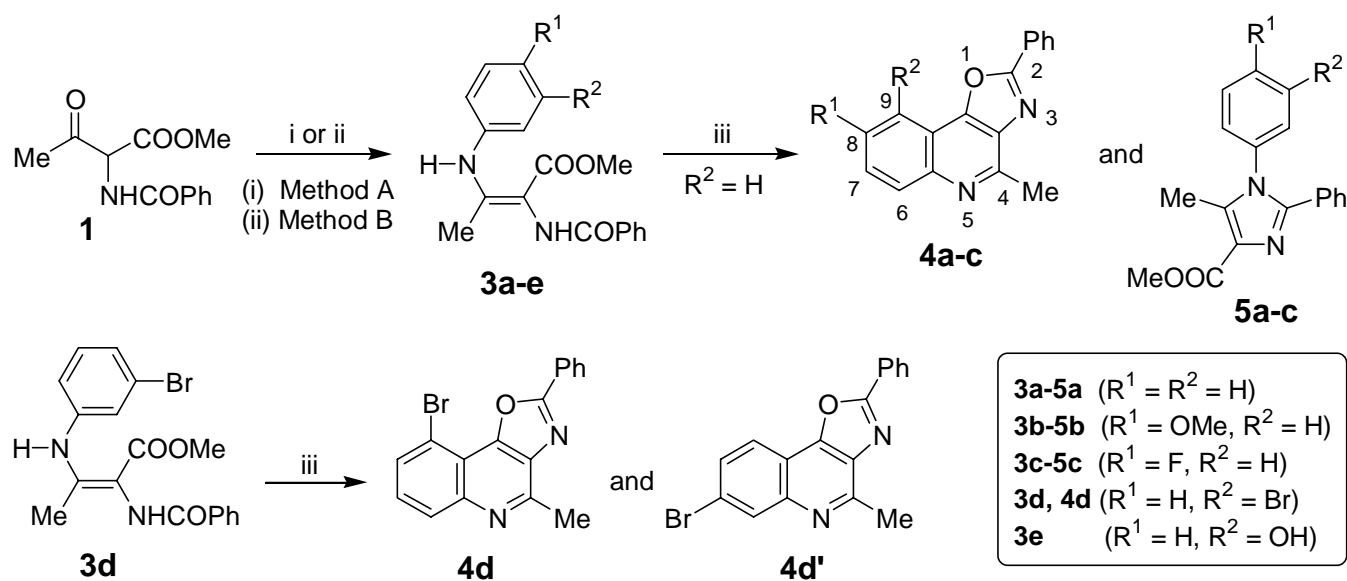
There has been only a limited number of syntheses of imidazoles described in the literature in which the acyclic precursors containing C–N–C–C–N structural element have been used.<sup>13</sup> They are cyclizations of  $\alpha$ -acylaminoamidines,<sup>14</sup>  $\alpha$ -acylaminothiocarboxylic acid amides,<sup>15</sup>  $\alpha$ -acylamino-carboxylic acids amides,<sup>16</sup> hydrazones,<sup>17</sup> *N*-substituted derivatives of  $\alpha$ -aminocarbonitriles,<sup>18</sup> *N*-substituted 1,2-diaminoalkanes,<sup>19</sup> and bisamides of oxalic acid.<sup>20</sup>

Substituted alkyl 2-acylamino-3-dimethylaminopropenoates and related compounds as masked

$\alpha$ -formyl- $\alpha$ -amino acids have turned out to be versatile reagents in the synthesis of many heterocyclic systems.<sup>21</sup> 3-Arylamino propenoates without 2-acylamino substituent have been found as suitable intermediates for the preparation of 1,4-dihydro-4-oxoquinoline derivatives.<sup>22</sup> The latter compounds have been further used also for the preparation of oxazoloquinoline derivatives.<sup>23</sup> In connection with this research, methyl 2-benzoylamino-3-oxobutanoate (**1**), prepared from hippuric acid by treatment with *N,N*-dimethylacetamide in the presence of phosphoryl chloride, followed by hydrolysis with hydrochloric acid in methanol, has been employed for the synthesis of 1-substituted 4-benzoylamino-3-methyl-5(2*H*)-pyrazolones.<sup>24</sup>

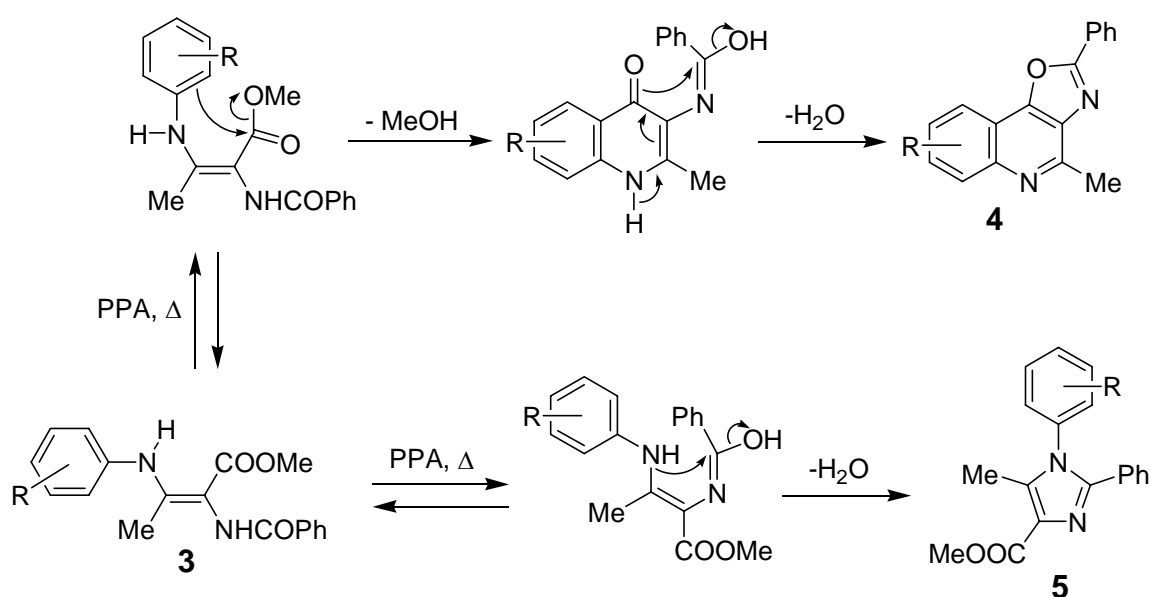
## RESULTS AND DISCUSSION

In this paper we report on the transformation of **1** with aromatic amines (**2a–e**) into methyl 3-arylamino-2-benzoylamino-2-enoates (**3a–e**) by heating for several hours in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA), either in benzene (method A) or in ethanol (Method B), with yields 52–79% in ethanol and 9–74% in benzene. Heteroaromatic amines, such as 2-aminopyridine, 2-amino-4-methylpyridine, and 2-amino-5-chloropyridine did not react under these conditions. When compounds (**3a–c**) were heated in polyphosphoric acid (PPA) at 130–140°C for 1–2.5 h, followed by neutralization of the reaction mixture with saturated solution of sodium hydrogen carbonate two products were isolated in each case. Both components were separated by column chromatography to give 2-phenyl-4-methyl-oxazolo[4,5-*c*]quinoline derivatives (**4a–c**) and 1-aryl-5-methyl-1*H*-imidazole-4-carboxylates (**5a–c**) in moderate yields. In the case of **3d**, the isomeric 7-bromo- (**4d**) and 9-bromo-4-methyl-2-phenyl-oxazolo[4,5-*c*]quinoline (**4d'**) were isolated in 14 and 24% yields, respectively (Scheme 1).



Scheme 1. (i) Ar-NH<sub>2</sub> (**2a–e**), benzene, PTSA (cat.), reflux, Dean-Stark (Method A); (ii) Ar-NH<sub>2</sub> (**2a–e**), EtOH, PTSA (cat.), reflux (Method B); (iii) PPA, 130–140°C, then chromatographic separation.

The formation of the products can be explained in the following way. The cyclization of compounds (**3**) can take place between the methoxycarbonyl group and aromatic ring at *ortho* position in regard to the amino group to form 3-benzoylamino substituted 4-oxo-1,4-dihydroquinoline intermediate followed by cyclodehydration taking place between benzoylamino and potential hydroxy group at the 4 position in quinoline ring to give oxazolo[4,5-*c*]quinoline derivatives (**4**). This latter reaction is analogous to the cyclization of 3-amino-4-oxo-1,2-dihydroquinoline in the presence of acetic anhydride reported recently.<sup>1x</sup> The concurrent reaction is cyclization taking place between the amino group attached to the aromatic ring and carbonyl group of the benzoylamino group to give imidazole derivatives (**5**) (Scheme 2).



Scheme 2

The structures of new compounds are based on elemental analyses, <sup>1</sup>H NMR spectra, MS spectral data and X-Ray determination. The <sup>1</sup>H NMR spectra of compounds (**3**) exhibit only one set of signals. The NOESY spectrum of **3b** in DMSO-*d*<sub>6</sub> at 302 K shows the NOE between the protons of the methyl group attached to the double bond and proton attached to the nitrogen atom of the benzoylamino group on one side, and between the proton attached to the nitrogen atom of the arylamino group and the protons of the methoxycarbonyl group, thus indicating that compounds (**3**) exist in the (*E*)-configuration (Figure 1).

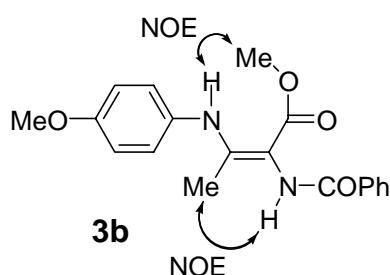


Figure 1

The structures of compounds (**4**) were determined by  $^1\text{H}$  NMR spectra. Compound (**4a**) shows besides five protons of the 2-phneyl group four aromatic protons belonging to thequinoline ring. Compounds (**4a-c**) show three protons for quinoline part of the molecule with the corresponding coupling constants indicating that the substituents are attached at 8-position. Compound (**4d**) exhibits three protons for quinoline nucleus at  $\delta = 7.55$  ppm ( $\text{H}_7$ ), 7.87 ppm ( $\text{H}_8$ ) and 8.15 ppm ( $\text{H}_6$ ) with the coupling contants  $J_{6,7} = 8.5$  Hz,  $J_{6,8} = 1.0$  Hz, and  $J_{7,8} = 7.6$  Hz, confirming that the bromine is attached at 9-position. Compound (**6d**) exhibits three protons at  $\delta = 7.73$  ppm ( $\text{H}_8$ ), 8.11 ppm ( $\text{H}_9$ ), and 8.37 ( $\text{H}_6$ ) with the coupling constants  $J_{6,8} = 1.9$  Hz,  $J_{6,9} = 0.4$  Hz, and  $J_{8,9} = 8.6$  Hz indeicating that the bromine is attached at 7-position. The structure of compound (**4c**) was confirmed also by X-Ray analysis (Figure 2).

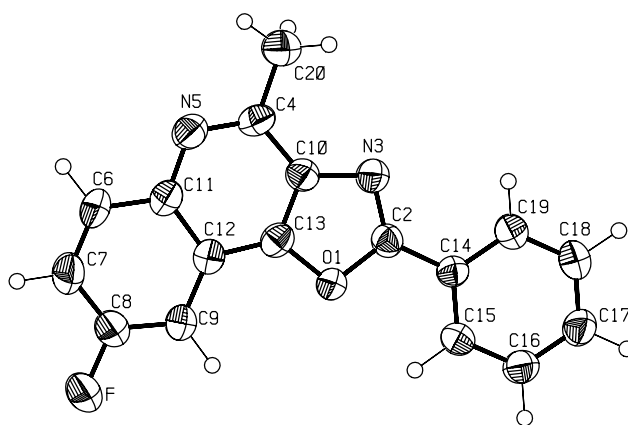


Figure 2. The asymmetric unit showing atom labels of the non-hydrogen atoms. Ellipsoids are plotted at 50% probability level.

Compounds (**5**) show besides the aromatic protons for groups attached at 1- and 2-postion a singlet in the range at  $\delta = 2.40$ – $2.41$  ppm for the methyl group at 5-position and at  $\delta = 3.86$ – $3.95$  ppm for ester methyl group at 4-position.

### X-Ray Structure Determination

$\text{C}_{17}\text{H}_{11}\text{N}_2\text{OF}$ ,  $M_r=278.3$ , monoclinic  $P2_1$ , No.: 4,  $a=3.84190(10)$ ,  $b=10.8035(3)$ ,  $c=15.7459(6)$  Å,  $V=653.12(4)$  Å<sup>3</sup>,  $Z=2$ ,  $D_x=1.415$  Mg/m<sup>3</sup>, MoK $\alpha$  radiation,  $\lambda=0.71069$  Å,  $\mu=0.10$  mm<sup>-1</sup>.

Diffraction data were collected on the Nonius-Kappa CCD Diffractometer at room temperature using graphite monochromatized MoK $\alpha$  radiation. The crystal dimensions were  $0.20 \times 0.15 \times 0.50$  mm. The entire reciprocal sphere was covered by  $\phi$  and  $\omega$  scans of  $2^\circ$  per frame. The data collection was performed using the Nonius Collect Software<sup>25</sup> while the indexing and scaling of the data were performed using

DENZO and SCALEPACK.<sup>26</sup> The merging of the reflections up to the minimum  $d$  value of 0.77 Å gave  $R_{\text{int}}=0.040$  for 1549 unique reflections of which 1035 were observed ( $I > 1.5\sigma(I)$ ). Absorption correction was not performed due to small absorption coefficient.

The structure was solved using SIR92 program<sup>27</sup> while the refinement and plotting were done using Xtal3.4<sup>28</sup> program package. The solution program provided all non-hydrogen atoms, which were refined with anisotropic displacement factors. The hydrogen atoms could be found among the peaks in the difference Fourier map but were not stable in the refinement. They were stabilized using restraints on bond lengths and angles. Regina weighting scheme<sup>29</sup> was applied. The refinement of 214 variables on  $F_o$  magnitudes of 1035 reflections and 33 restraints ended with  $R=0.054$ ,  $R_w=0.057$ . Maximal shift/error was 0.051 and maximal and minimal residual electron densities in the difference Fourier map were 0.37 and  $-0.32 \text{ e}/\text{Å}^3$ .

Final atomic coordinates and equivalent atomic displacement parameters are given in Table 1, bond distances and angles are presented in Table 2. The asymmetric unit with atom labels is shown in Figure 2. It consists of one planar molecule. No unusual short contacts were found in the packing diagram.

Table 1. Fractional Coordinates and Equivalent Temperature Factors ( $\text{Å}^2$ ).  $U_{\text{eq}}$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

|       | x/a        | y/b        | z/c       | $U_{\text{eq}}$ |
|-------|------------|------------|-----------|-----------------|
| F     | 0.8946(15) | -0.1979(7) | 0.1288(2) | 0.101(3)        |
| O(1)  | 0.4578(9)  | 0.1482(8)  | 0.3405(2) | 0.046(2)        |
| N(3)  | 0.3776(11) | 0.3555(8)  | 0.3298(3) | 0.048(2)        |
| N(5)  | 0.7081(13) | 0.3075(8)  | 0.1134(3) | 0.053(3)        |
| C(2)  | 0.3597(12) | 0.2577(9)  | 0.3787(3) | 0.043(3)        |
| C(4)  | 0.5814(12) | 0.3709(9)  | 0.1781(3) | 0.048(3)        |
| C(6)  | 0.8852(15) | 0.1171(9)  | 0.0514(3) | 0.057(3)        |
| C(7)  | 0.9320(18) | -0.0094(9) | 0.0546(3) | 0.066(4)        |
| C(8)  | 0.8448(18) | -0.0727(8) | 0.1275(4) | 0.065(4)        |
| C(9)  | 0.7210(16) | -0.0170(8) | 0.1980(3) | 0.057(3)        |
| C(10) | 0.5003(14) | 0.3103(8)  | 0.2542(3) | 0.045(3)        |
| C(11) | 0.7509(14) | 0.1812(8)  | 0.1210(3) | 0.049(3)        |
| C(12) | 0.6703(14) | 0.1117(9)  | 0.1952(3) | 0.047(3)        |
| C(13) | 0.5478(13) | 0.1849(8)  | 0.2598(3) | 0.045(3)        |
| C(14) | 0.2591(13) | 0.2510(9)  | 0.4663(3) | 0.042(2)        |
| C(15) | 0.3168(14) | 0.1453(9)  | 0.5142(3) | 0.048(3)        |
| C(16) | 0.2279(16) | 0.1424(9)  | 0.5987(3) | 0.056(3)        |
| C(17) | 0.0777(16) | 0.2443(9)  | 0.6355(3) | 0.057(3)        |
| C(18) | 0.0201(14) | 0.3505(9)  | 0.5882(3) | 0.054(3)        |
| C(19) | 0.1123(13) | 0.3546(8)  | 0.5038(3) | 0.048(3)        |
| C(20) | 0.5304(9)  | 0.5073(4)  | 0.1679(2) | 0.069(4)        |

Table 2: Bond Distances (Å) and Bond Angles(°) with e.s.d.'s in parentheses.

|                  |           |                   |           |
|------------------|-----------|-------------------|-----------|
| F-C(8)           | 1.366(12) | C(7)-C(8)         | 1.389(10) |
| O(1)-C(2)        | 1.385(11) | C(8)-C(9)         | 1.363(9)  |
| O(1)-C(13)       | 1.387(7)  | C(9)-C(12)        | 1.404(13) |
| N(3)-C(2)        | 1.310(11) | C(10)-C(13)       | 1.370(13) |
| N(3)-C(10)       | 1.386(8)  | C(11)-C(12)       | 1.433(9)  |
| N(5)-C(4)        | 1.334(9)  | C(12)-C(13)       | 1.384(9)  |
| N(5)-C(11)       | 1.378(13) | C(14)-C(15)       | 1.382(12) |
| C(2)-C(14)       | 1.449(6)  | C(14)-C(19)       | 1.394(11) |
| C(4)-C(10)       | 1.410(9)  | C(15)-C(16)       | 1.386(7)  |
| C(4)-C(20)       | 1.495(10) | C(16)-C(17)       | 1.380(12) |
| C(6)-C(7)        | 1.379(14) | C(17)-C(18)       | 1.382(12) |
| C(6)-C(11)       | 1.411(9)  | C(18)-C(19)       | 1.389(7)  |
|                  |           |                   |           |
| C(2)-O(1)-C(13)  | 103.6(7)  | N(5)-C(11)-C(6)   | 117.7(6)  |
| C(2)-N(3)-C(10)  | 104.3(7)  | N(5)-C(11)-C(12)  | 124.1(6)  |
| C(4)-N(5)-C(11)  | 119.2(6)  | C(6)-C(11)-C(12)  | 118.2(8)  |
| O(1)-C(2)-N(3))  | 114.4(5)  | C(9)-C(12)-C(11)  | 120.7(6)  |
| O(1)-C(2)-C(14)  | 117.2(7)  | C(9)-C(12)-C(13)  | 126.4(6)  |
| N(3)-C(2)-C(14)  | 128.4(8)  | C(11)-C(12)-C(13) | 112.9(8)  |
| N(5)-C(4)-C(10)  | 120.5(8)  | O(1)-C(13)-C(10)  | 107.7(6)  |
| N(5)-C(4)-C(20)  | 118.3(6)  | O(1)-C(13)-C(12)  | 127.8(8)  |
| C(10)-C(4)-C(20) | 121.2(6)  | C(10)-C(13)-C(12) | 124.5(6)  |
| C(7)-C(6)-C(11)  | 120.6(6)  | C(2)-C(14)-C(15)  | 121.2(7)  |
| C(6)-C(7)-C(8)   | 118.9(6)  | C(2)-C(14)-C(19)  | 119.3(7)  |
| F-C(8)-C(7)      | 117.5(6)  | C(15)-C(14)-C(19) | 119.5(5)  |
| F-C(8)-C(9)      | 118.6(6)  | C(14)-C(15)-C(16) | 120.2(7)  |
| C(7)-C(8)-C(9)   | 123.9(8)  | C(15)-C(16)-C(17) | 120.4(7)  |
| C(8)-C(9)-C(12)  | 117.7(6)  | C(16)-C(17)-C(18) | 119.9(5)  |
| N(3)-C(10)-C(4)  | 131.2(8)  | C(17)-C(18)-C(19) | 120.1(7)  |
| N(3)-C(10)-C(13) | 110.0(6)  | C(14)-C(19)-C(18) | 120.0(7)  |
| C(4)-C(10)-C(13) | 118.8(6)  |                   |           |

## EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The  $^1\text{H}$  NMR spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer with  $\text{CDCl}_3$  as solvent and TMS as the internal standard. Mass spectra were obtained on an Autospeck Q spectrometer. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyser 2400. Column chromatography was performed on silica gel (Silica gel 60, 0.035–0.070 mm, Fluka).

Methyl 2-benzoylamino-3-oxobutanoate (**1**) was prepared according to the procedure reported in the literature.<sup>24</sup>

### General Procedure for the Preparation of Methyl 2-Benzoylamino-3-arylamino-2-enoates (**3**).

**Procedure A.** A mixture of aromatic amine (**2**) (0.001 mol), methyl 2-benzoylamino-3-oxobutanoate (**1**) (0.235 g, 0.001 mol), benzene (5 mL), and a catalytic amount of PTSA was heated under reflux for 1–11.5

h. A Dean-Stark water trap was used to remove the water formed during the reaction. The volatile components were evaporated *in vacuo*, the residue was triturated with diethyl ether (3 mL) or ethanol (4 mL), cooled, and the precipitate was collected by filtration to give **3**.

**Procedure B.** A mixture of aromatic amine (**2**) (0.001 mol), methyl 2-benzoylamino-3-oxobutanoate (**1**) (0.235 g, 0.001 mol), ethanol (4 mL), and a catalytic amount of PTSA was heated under reflux for 4–11.5 h. The volatile components were evaporated *in vacuo*, the residue was triturated with ether (3 mL) or ethanol (3 mL), cooled, and the precipitate was collected by filtration to give **3**.

The following compounds were prepared in this manner:

**Methyl 3-Anilino-2-benzoylamino-but-2-enoate (3a).** This compound was prepared from **1** and aniline (**2a**) (0.093 g, 0.001 mol), reflux for 11 h (Procedure A) or 14 h (Procedure B); trituration with ether. Yield: 0.245 g (79%, Procedure A) or 0.158 g (51%, Procedure B); mp 129–133°C (from ethanol). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.08 (3H, s, CH<sub>3</sub>), 3.72 (3H, s, OCH<sub>3</sub>), 7.04 (1H, br s, NH), 7.11–7.23 (3H, m, Ph), 7.31–7.39 (2H, m, Ph), 7.44–7.57 (3H, m, Ph), 7.85–7.91 (2H, m, Ph), 10.83 (1H, br s, NH). *Anal.* Calcd for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.83; H, 5.97; N, 9.11.

**Methyl 2-Benzoylamino-3-[(4-methoxyphenyl)amino]but-2-enoate (3b).** This compound was prepared from **1** and 4-methoxyaniline (**2b**) (0.123 g, 0.001 mol), reflux for 4 h (Procedure A) or 11.5 h (Procedure B); trituration with ether. Yield: 0.252 g (74%, Procedure A) or 0.225 g (66%, Procedure B); mp 122–126°C (from mixture of diethyl ether and ethanol). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.99 (3H, s, CH<sub>3</sub>), 3.71 (3H, s, OCH<sub>3</sub>), 3.81 (3H, s, 4-OCH<sub>3</sub>), 6.88 (2H, d, *J* = 8.7 Hz, 2H of Ar), 7.02 (1H, br s, NH), 7.08 (2H, d, *J* = 8.7 Hz, 2H of Ar), 7.43–7.57 (3H, m, Ph), 7.84–7.90 (2H, m, Ph), 10.63 (1H, br s, NH). *Anal.* Calcd for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.19; H, 6.04; N, 8.41.

**Methyl 2-Benzoylamino-3-[(4-fluorophenyl)amino]but-2-enoate (3c).** This compound was prepared from **1** and 4-fluoroaniline (**2c**) (0.111 g, 0.001 mol), reflux for 3.5 h (Procedure A) or 4 h (Procedure B); trituration with ethanol. Yield: 0.184 g (56%, Procedure A) or 0.246 g (75%, Procedure B); mp 170–173°C (from ethanol). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.01 (3H, s, CH<sub>3</sub>), 3.72 (3H, s, OCH<sub>3</sub>), 7.01–7.15 (5H, m, C<sub>6</sub>H<sub>4</sub> and NH), 7.44–7.58 (3H, m, Ph), 7.84–7.90 (2H, m, Ph), 10.69 (1H, br s, NH). *Anal.* Calcd for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub>F: C, 65.84; H, 5.22; N, 8.53. Found: C, 65.78; H, 5.34; N, 8.45.

**Methyl 2-Benzoylamino-3-[(3-bromophenyl)amino]but-2-enoate (3d).** This compound was prepared from **1** and 3-bromoaniline (**2d**) (0.172 g, 0.001 mol), reflux for 5 h (Procedure A) or 6.5 h (Procedure B); trituration with ethanol. Yield: 0.035 g (9%, Procedure A) or 0.202 g (52%, Procedure B); mp 143–148°C

(from ethanol).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.09 (3H, s,  $\text{CH}_3$ ), 3.72 (3H, s,  $\text{OCH}_3$ ), 7.04 (1H, br s, NH), 7.07 (1H, m,  $J = 1.1, 1.5, 7.9$  Hz, 1H of Ar), 7.21 (1H, dd,  $J = 7.9, 8.7$  Hz, 1H of Ar), 7.29–7.34 (2H, m,  $J = 1.1, 1.5, 8.7$  Hz, 2H of Ar), 7.45–7.58 (3H, m, Ph), 7.85–7.90 (2H, m, Ph), 10.83 (1H, br s, NH). *Anal.* Calcd for  $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_3\text{Br}$ : C, 55.54; H, 4.40; N, 7.20. Found: C, 55.65; H, 4.52; N, 7.00.

**Methyl 2-Benzoylamino-3-[(3-hydroxyphenyl)amino]but-2-enoate (3e).** This compound was prepared from **1** and 3-hydroxyaniline (**2e**) (0.109 g, 0.001 mol), reflux for 1 h (Procedure A) or 8 h (Procedure B); trituration with ethanol. Yield: 0.101 g (31%, Procedure A) or 0.150 g (46%, Procedure B); mp 175–179°C (from ethanol).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.07 (3H, s,  $\text{CH}_3$ ), 3.64 (3H, s,  $\text{OCH}_3$ ), 6.28 (1H, br s, OH), 6.36–6.70 (3H, m, 3H of Ar), 7.12 (1H, br s, NH), 7.16 (1H, m, 1H of Ar), 7.45–7.58 (3H, m, Ph), 7.85–7.92 (2H, m, Ph), 10.76 (1H, br s, NH). *Anal.* Calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$ : C, 66.25; H, 5.56; N, 8.58. Found: C, 66.02; H, 5.63; N, 8.69.

**General Procedure for the Preparation of Substituted 4-Methyl-2-phenyl[1,3]oxazolo[4,5-*c*]quinolines (4) and Methyl 1-Aryl-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylates (5).** A mixture of methyl 3-arylamino-2-benzoylamino-but-2-enoate (**3**) (0.001 mol) and PPA (1.5 g) was heated at 130–140°C for 50 min–2.5 h. The solution was cooled and the saturated aqueous solution of  $\text{NaHCO}_3$  (20–30 mL) was added. The precipitate was collected by filtration and the crude mixture of **4** and **5** was separated and purified by column chromatography. Fractions containing the products **4** and **5** were combined, respectively, and evaporated *in vacuo* to give analytically pure compounds (**4**) and (**5**). The following compounds were prepared in this manner:

**4-Methyl-2-phenyl[1,3]oxazolo[4,5-*c*]quinoline (4a) and Methyl 5-Methyl-1,2-diphenyl-1*H*-imidazole-4-carboxylate (5a).** A mixture of **4a** and **5a** was prepared from methyl 3-anilino-2-benzoylamino-but-2-enoate (**2a**) (0.310 g, 0.001 mol) and PPA, heating for 50 min. Column chromatography: first **4a** (petroleum ether–ethyl acetate, 5:1), then **5a** (ethyl acetate).

Compound (**4a**). Yield: 0.052 g (20%); mp 158–161°C; MS:  $m/z = 260$  ( $\text{M}^+$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.05 (3H, s,  $\text{CH}_3$ ), 7.55–7.60 (3H, m, Ph), 7.63 (1H, ddd,  $J = 1.2, 7.0, 8.1$  Hz,  $\text{H}_7$ ), 7.73 (1H, ddd,  $J = 1.5, 7.0, 8.5$  Hz,  $\text{H}_8$ ), 8.18 (1H, ddd,  $J = 0.7, 1.2, 8.5$  Hz,  $\text{H}_9$ ), 8.25 (1H, ddd,  $J = 0.7, 1.5, 8.1$  Hz,  $\text{H}_6$ ), 8.33–8.38 (2H, m, Ph). *Anal.* Calcd for  $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}$ : C, 78.44; H, 4.65; N, 10.76. Found: C, 78.48; H, 4.65; N, 11.00.

Compound (**5a**): Yield: 0.041 g (14%); mp 132–135°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.41 (3H, s,  $\text{CH}_3$ ), 3.95 (3H, s,  $\text{OCH}_3$ ), 7.15–7.25 (5H, m, Ph), 7.34–7.38 (2H, m, Ph), 7.45–7.50 (3H, m, Ph). *Anal.* Calcd for  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2$ : C, 73.95; H, 5.52; N, 9.58. Found: C, 73.74; H, 5.71; N, 9.31.



**8-Methoxy-4-methyl-2-phenyl[1,3]oxazolo[4,5-*c*]quinoline (4b) and Methyl 1-(4-Methoxyphenyl)-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (5b).** A mixture of **4b** and **5b** was prepared from methyl 2-benzoylamino-3-[(4-methoxyphenyl)amino]but-2-enoate (**3b**) (0.340 g, 0.001 mol) and PPA, heating for 1 h. Column chromatography: first **4b** (petroleum ether–ethyl acetate, 5:1), then **5b** (ethyl acetate). Microanalyses for C, H, and N for compounds (**4b**) and (**5b**) were not completely satisfactory. The best values are given below. The identity of compounds was confirmed by HRMS.

Compound (**4b**). Yield: 0.038 g (13%); mp 140–142°C. MS:  $m/z = 290$  ( $M^+$ ), HRMS: Calcd: 290.106350, Found: 290.105528.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.00 (3H, s,  $\text{CH}_3$ ), 4.02 (3H, s,  $\text{OCH}_3$ ), 7.36 (1H, dd,  $J = 3.0, 9.4$  Hz,  $\text{H}_7$ ), 7.48 (1H, d,  $J = 3.0$  Hz,  $\text{H}_9$ ), 7.56–7.60 (3H, m, Ph), 8.06 (1H, d,  $J = 9.4$  Hz,  $\text{H}_6$ ), 8.34–8.39 (2H, m, Ph). *Anal.* Calcd for  $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_2$ : C, 74.47; H, 4.86; N, 9.65. Found: C, 73.94; H, 5.02; N, 9.13.

Compound (**5b**). Yield: 0.029 g (9%); mp 137–141°C. MS:  $m/z = 322$  ( $M^+$ ), HRMS: Calcd: 322.132540, Found: 322.131743.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.40 (3H, s,  $\text{CH}_3$ ), 3.86 (3H, s,  $\text{OCH}_3$ ), 3.95 (3H, s,  $\text{OCH}_3$ ), 6.96 (2H, d,  $J = 9.0$  Hz, 2H of Ar), 7.09 (2H, d,  $J = 9.0$  Hz, 2H of Ar), 7.17–7.27 (3H, m, Ph), 7.37–7.41 (2H, m, Ph). *Anal.* Calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$ : C, 70.79; H, 5.63; N, 8.69. Found: C, 70.24; H, 5.92; N, 8.11.

**8-Fluoro-4-methyl-2-phenyl[1,3]oxazolo[4,5-*c*]quinoline (4c) and Methyl 1-(4-Fluorophenyl)-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (5c).** A mixture of **4c** and **5c** was prepared from methyl 2-benzoylamino-3-[(4-fluorophenyl)amino]but-2-enoate (**3c**) (0.328 g, 0.001 mol) and PPA, heating for 2.5 h. Column chromatography (ether): first **4c** then **5c**.

Compound (**4c**). Yield: 0.181 g (65%); mp 168–170°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.05 (3H, s,  $\text{CH}_3$ ), 7.43–7.50 (1H, ddd,  $J_{\text{H}_6\text{H}_7} = 9.0, J_{\text{H}_7\text{H}_9} = 3.0, {}^3J_{\text{FH}_7} = 8.7$  Hz,  $\text{H}_7$ ), 7.55–7.61 (3H, m, Ph), 7.83 (1H, dd,  $J_{\text{H}_7\text{H}_9} = 3.0, {}^3J_{\text{FH}_9} = 8.7$  Hz,  $\text{H}_9$ ), 8.16 (1H, dd,  $J_{\text{H}_6\text{H}_7} = 9.0, {}^4J_{\text{FH}_6} = 5.1$  Hz,  $\text{H}_6$ ), 8.32–8.37 (2H, m, Ph). *Anal.* Calcd for  $\text{C}_{17}\text{H}_{11}\text{N}_2\text{OF}$ : C, 73.37; H, 3.98; N, 10.07. Found: C, 73.32; H, 3.82; N, 9.98.

Compound (**5c**). Yield: 0.099 g (32%); mp 188–190°C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.41 (3H, s,  $\text{CH}_3$ ), 3.95 (3H, s,  $\text{OCH}_3$ ), 7.17 (4H, m,  $\text{C}_6\text{H}_4$ ), 7.20–7.27 (3H, m, Ph), 7.32–7.37 (2H, m, Ph). *Anal.* Calcd for  $\text{C}_{18}\text{H}_{15}\text{N}_2\text{OF}$ : C, 69.67; H, 4.87; N, 9.03. Found: C, 69.74; H, 4.63; N, 8.93.

**9-Bromo-4-methyl-2-phenyl[1,3]oxazolo-[4,5-*c*]quinoline (6d) and 7-Bromo-4-methyl-2-phenyl-[1,3]oxazolo[4,5-*c*]quinoline (4d')** A mixture of **4d** and **4d'** was prepared from methyl 2-benzoylamino-3-[(3-bromophenyl)amino]but-2-enoate (**3d**) (0.389 g, 0.001 mol) and PPA, heating for 1.5 h. Column chromatography: first **4d** (petroleum ether–ethyl acetate, 5:1) then **4d'** (ethyl acetate).

Compound (**4d**). Yield: 0.047 g (14%); mp 195–196°C. MS:  $m/z = 338$  ( $M^+$ ), 340 ( $M^+ + 2$ ).  $^1\text{H NMR}$  (300

MHz, CDCl<sub>3</sub>):  $\delta$  3.03 (3H, s, CH<sub>3</sub>), 7.55–7.61 (3H, m, Ph), 7.73 (1H, dd,  $J = 1.9, 8.6$  Hz, H<sub>8</sub>), 8.11 (1H, dd,  $J = 0.4, 8.6$  Hz, H<sub>9</sub>), 8.31–8.37 (2H, m, Ph), 8.37 (1H, dd,  $J = 0.4, 1.9$  Hz, H<sub>6</sub>). *Anal.* Calcd for C<sub>17</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub>Br: C, 60.20; H, 3.27; N, 8.26. Found: C, 60.48; H, 3.07; N, 8.20.

Compound (**4d'**). Yield: 0.081 g (24%); mp 185–186°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  3.05 (3H, s, CH<sub>3</sub>), 7.55 (1H, dd,  $J = 7.6, 8.5$  Hz, H<sub>7</sub>), 7.57–7.62 (3H, m, Ph), 7.87 (1H, dd,  $J = 1.0, 7.6$  Hz, H<sub>8</sub>), 8.15 (1H, dd,  $J = 1.0, 8.5$  Hz, H<sub>6</sub>), 8.35–8.41 (2H, m, Ph). *Anal.* Calcd for C<sub>17</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub>Br: C, 60.20; H, 3.27; N, 8.26. Found: C, 60.36; H, 3.04; N, 8.19.

## ACKNOWLEDGEMENTS

The financial support from the Ministry of Education, Science and Sport, Slovenia, through grant PS-0502-0103, is gratefully acknowledged. The crystallographic dataset was collected on the Kappa CCD Nonius diffractometer in the Laboratory of Inorganic Chemistry, Faculty of Chemistry and chemical Technology, University of Ljubljana, Slovenia. We acknowledge with thanks the financial contribution of the Ministry of Science and technology, Republic of Slovenia through grant Packet X-2000 and PS-511-102, which thus made the purchase of the apparatus possible.

## REFERENCES

1. J. R. Merchant and S. S. Shirali, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 3075; J. R. Merchant, M. S. Venkatesh, and S. S. Shirali, *Curr. Sci. India*, 1980, **49**, 20 (*Chem. Abstr.*, 1986, **92**, 181095u); O. A. Ponomarev, Yu. N. Brusilt'sev, V. Kh. Grif, and V. G. Mitina, *Ukr. Khim. Zh.*, 1990, **56**, 272; I. V. Ukrainets, S. G. Taran, L. V. Sidorenko, O. V. Gorokhova, and A. V. Turov, *Khim. Geterotsykl. Soed.*, 1997, 1536; M. Rehwald, P. Bellmann, T. Jeschke, and K. Gewald, *J. Prakt. Chem.-Chem. Ztg.*, 2000, **342**, 371.
2. M. Suzuki, K. Matsumoto, M. Miyoshi, N. Yoneda, and R. Ishida, *Chem. Pharm Bull.*, 1977, **25**, 2602.
3. H. H. Zoorob and W. S. Hamama, *Egypt. J. Chem.*, 1986, **29**, 325 (*Chem. Abstr.*, 1987, **111**, 7259a).
4. W. Steinschiffer, W. Fiala, W. Stadlbauer, *J. Heterocycl. Chem.*, 1994, **31**, 1647.
5. J. M. Schaus and R. D. Titus, Eli Lilly Co., U. S. Patent 4,659,832 (1987) (*Chem. Abstr.*, 1987, **107**, 23329); B. W. Caprothe and J. C. Jaen, Warner Lambert Co., European Patent Appl. 260,642 (1988) (*Chem. Abstr.*, 1988, **109**, 92992v).
6. D. L. Decktor, L. R. Fitzpatrick, and H. F. Campbell, Rover Pharmaceutical Corporation, US Patent 4,831,040 (1989) (*Chem. Abstr.*, 1990, **112**, 16278p).
7. Y. Inamoto, S. Kawai, K. Saneda, and T. Endo, Fuji Chemical Industry Co. Ltd., Japan Kokai Tokyo 03 109 388 [91 109388] (*Chem. Abstr.*, 1991, **115**, 279995).
8. J. H. Musser and R. E. Brown, USV Pharmaceutical Corporation, US Patent 4,563,463 (1986) (*Chem. Abstr.*, 1987, **106**, 50187).

9. A. Renaud, A. R. Schoofs, J. M. Guiraudie, and S. A. Delalande, European Patent Appl. 322263 (1989) (*Chem. Abstr.*, 1990, **112**, 216909g).
10. G. Brill, H. Hagen, K. O. Westphalen, and B. Würzer, BASF AG European Patent Appl. 401582 (1990) (*Chem. Abstr.*, 1991, **114**, 122372r).
11. G. X. Zhang, L. Y. Yu, F. D. Shi, B. G. Xiao, J. Bjork, G. Hedlund, and H. Link, *J. Neuroimmunol.*, 1997, **73**, 175; S. Hortelano, M. J. M. Diaz Guerra, A. Gonzalez Garcia, E. Leonardo, C. Gamallo, L. Bosca, and A. C. Martinez, *J. Immunol.*, 1997, **158**, 1402; S. Morecki, C. Nabet, P. Falk, M. Fridkis-Hareli, I. Pecht, J. J. Mond, and S. Slavin, *Autoimmunity*, 1997, **25**, 223; S. Bailly, M. Fay, and M. A. Gougerot-Pocidallo, *Pathol-Biol* 1993, **41**, 838.
12. J. F. Gerster, K. J. Lindstrom, G. J. Marszalek, B. A. Merrill, J. W. Mickelson, and M. J. Rice, 3M Innovative Properties Company, USA PCT Int. Appl. WO 00 6577 (*Chem. Abstr.*, 2000, **132**, 137381).
13. For reviews see: K. Ebel, in Houben-Weyl Methoden der Organischen Chemie, Band E8c, Heterarene III/Teil 3, Georg Thieme Verlag, Stuttgart, 1994, pp. 1–215; M. R. Grimmett, in 'Comprehensive Heterocyclic Chemistry', Vol 5, ed. by K. T. Potts, Pergamon Press, Oxford 1984, pp. 447–498; c) M. R. Grimmett, in 'Comprehensive Heterocyclic Chemistry II', Vol 3, ed. by I. Shinkai, Elsevier, Oxford 1996, pp. 77–220; W. Stadlbauer, in Science of Synthesis, Houben-Weyl Methods of Molecular Transformations, Georg Thieme Verlag, Stuttgart, 2002, Vol. 12, pp. 227–324.
14. E. Shaw and D. W. Wooley, *J. Biol. Chem.*, 1949, **191**, 89; E. Shaw, *J. Am. Chem. Soc.*, 1958, **80**, 3899; A. K. Sen and S. Ray, *Indian J. Chem.*, 1976, **B14**, 346; E. Shaw, *J. Org. Chem.*, 1965, **30**, 3371.
15. A. Spaltenstein, T. P. Holler, and P. B. Hopkins, *J. Org. Chem.*, 1987, **52**, 2977.
16. P. Karrer and C. Gränacher, *Helv. Chim. Acta*, 1924, **7**, 763; B. Gränacher, V. Schelling, and E. Schlatter, *Helv. Chim. Acta*, 1925, **8**, 873.
17. N. Engel and W. Steglich, *Liebigs Ann. Chem.*, 1978, 1916.
18. R. S. Hosmane, F. N. Burnett, and M. S. Albert, *J. Org. Chem.*, 1984, **49**, 1212; U. Schöllkopf and K. Hantke, *Liebigs Ann. Chem.*, 1979, 1602.
19. R. F. Shuman, W. E. Shearin, and R. J. Tull, *J. Org. Chem.*, 1979, **44**, 4532; R. W. Begland, D. R. Hartter, F. N. Jones, D. J. Sam, W. A. Sheppard, O. W. Webster, and F. J. Weigert, *J. Org. Chem.*, 1974, **39**, 2341; Y. Ohtsuka, *J. Org. Chem.*, 1976, **41**, 629; D. Legroux, J.-P. Schoeni, C. Pont, and J.-P. Fleury, *Helv. Chim. Acta*, 1987, **70**, 187; U. Schöllkopf, P.-H. Porsch, and H.-H. Lau, *Liebigs Ann. Chem.*, 1979, 1444; H.-H. Lau and U. Schöllkopf, *Liebigs Ann. Chem.*, 1982, 2093.
20. O. Wallach, *Liebigs Ann. Chem.*, 1877, **184**, 33; O. Wallach, *Ber.*, 1883, **16**, 534; E. F. Godefroi, C. A. M. van der Eycken, and P. A. J. Janssen, *J. Org. Chem.*, 1967, **32**, 1259.
21. For recent reviews see: B. Stanovnik, *J. Heterocycl. Chem.*, 1999, **36**, 1581; B. Stanovnik and J. Svete,

- Synlett*, 2000, 1077; B. Stanovnik and J. Svete, *Targets in Heterocyclic Systems*, 2000, **4**, 105; J. Svete, *J. Heterocycl. Chem.*, 2002, **39**, 437.
22. S. Trippitelli, M. Pierrot, J.-P. Gozard, and R. Gallo, *Heterocycl. Commun.* 1997, **3**, 363; H. Koga, A. Itoh, S. Murayama, S. Suzue, and T. Irikura, *J. Med. Chem.*, 1980, **23**, 1358; N. P. Peet, L. E. Baugh, S. Sunder, and J. E. Lewis, *J. Med. Chem.*, 1985, **28**, 298.
  23. A. Staskun, *J. Org. Chem.*, 1966, **31**, 2674; B. Stanovnik, A. Štimac, M. Tišler, and B. Verček, *Vestn. Slov. Kem Drus.* 1981, **28**, 427.
  24. U. Bratušek, A. Hvala, and B. Stanovnik, *J. Heterocycl. Chem.*, 1998, **35**, 1281.
  25. Collect Software. Nonius, BV, Delft, the Netherlands (1998).
  26. Z. Otwinowski and W. Minor, *Methods Enzymol.*, 1977, **276**, 307.
  27. A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, and G. Polidori, *J. Appl. Cryst.*, 1994, **27**, 435.
  28. S. R. Hall, G. S. D. King, and J. M. Stewart, *The Xtal3.4 User's Manual*, University of Western Australia, Lamb, Perth, 1995.
  29. H. Wang and B. E. Robertson, *Structure and Statistics in Crystallography*, ed. by A. J. C. Wilson, Adenine Press, New York, 1985.