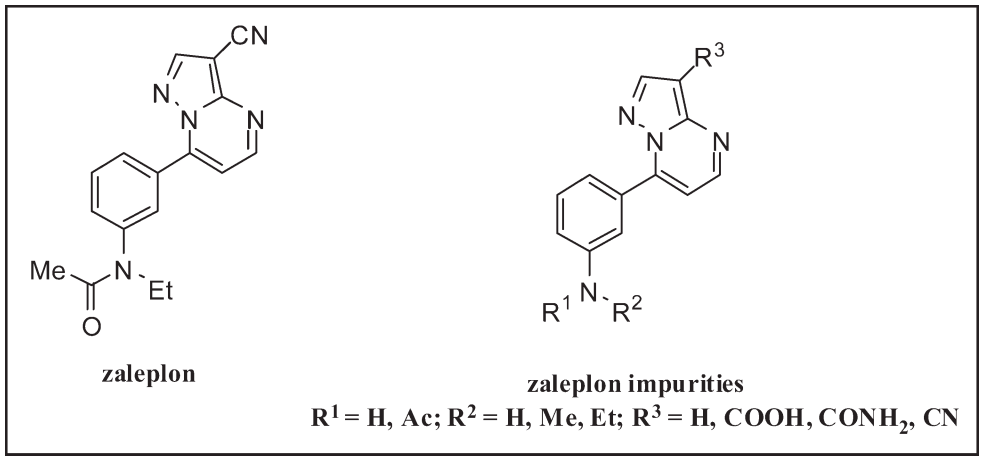
Stanislav Rádl,[a]* Michaela Blahovcová,[b] Lukáš Plaček,[a] Tomáš Pekárek,[a] and Jaroslav Havlíček[a]

[a]Zentiva, U kabelovny 130, 102 01 Prague 10, Czech Republic
[b]Pharmaceuticl Faculty of the Charles University, Heyrovského 1203, 500 05 Hradec Králové, Czech Republic
*E-mail: stanislav.radl@zentiva.cz

Received August 19, 2009
DOI 10.1002/jhet.335
Published online 20 January 2010 in Wiley InterScience (www.interscience.wiley.com).

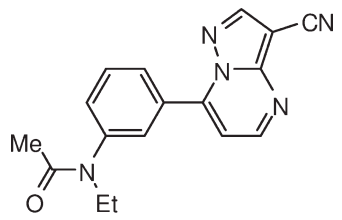


Synthesis of several potential impurities and/or degradation products of zaleplon is identified. All the prepared compounds were unambiguously identified by NMR techniques. Spectral characteristics (IR, UV, MS) of these compounds are also given.

J. Heterocyclic Chem., **47**, 276 (2010).

INTRODUCTION

Zaleplon (**1**) is a nonbenzodiazepine hypnotic belonging with zolpidem and zopiclon to the so-called Z-hypnotic class [1,2]. Clinical results have shown that zaleplon is efficacious in the treatment of insomnia where difficulty in falling asleep is the primary problem. Zaleplon unlike many other hypnotic drugs does not interfere with sleep architecture and can be administered for up to 5 weeks without the risk of dependence or rebound insomnia upon discontinuation [3].



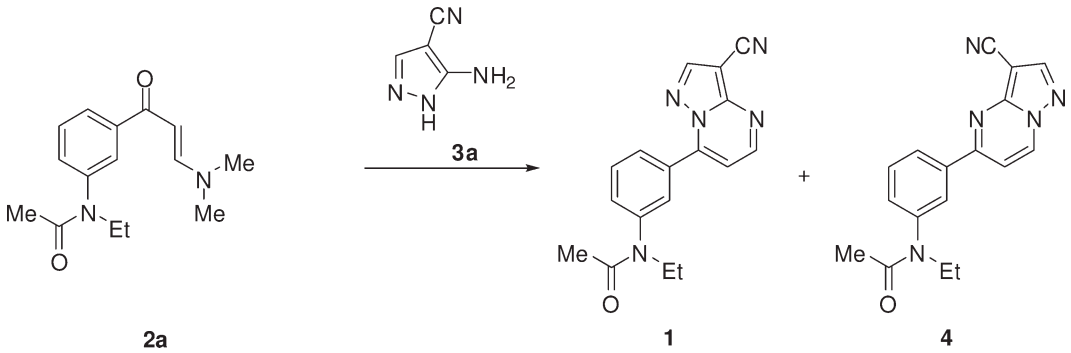
zaleplon (1)

Most of the described methods [4–7] of preparation of zaleplon are based on reaction of *N*-[3-[(2*E*)-3-(dimethylamino)prop-2-enoyl]phenyl]-*N*-ethylacetamide (**2a**) with 5-amino-1*H*-pyrazol-4-carbonitrile (**3a**) under acidic conditions. The original patent [4] describes the reaction in anhydrous acetic acid, but under these conditions considerable amounts of the corresponding isomer **4** is formed. Much better results are achieved using aqueous acetic [5] or formic [6] acids. Probably the best results regarding purity and yields are obtained when the reaction is done in aqueous alcohols in the presence of hydrochloric acid [7,8] (Scheme 1).

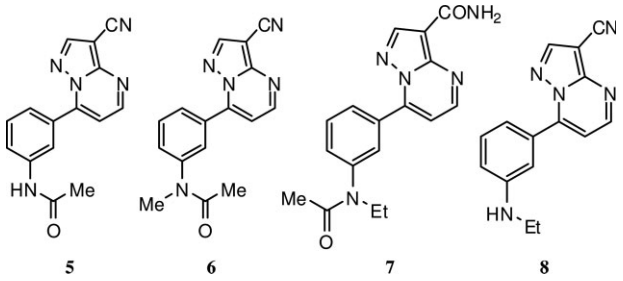
One of the principal parts of documentation of any active pharmaceutical ingredient (API) is description of impurities and/or degradation products which can be present. Identified impurities should be included in the specification when they are present at a level higher than the identification threshold, which is usually 0.10%. These impurities must be not only identified but also either isolated or independently synthesized.

Several impurities of zaleplon, including regioisomer **4** and compounds **5–8**, have recently been isolated and identified [9]. We have recently reported synthesis of zaleplon regioisomer **4** based on the Suzuki-Miyaura coupling [10]. To the best of our knowledge, no report on the synthesis of compounds **5–8** has been published

Scheme 1. Formation of zaleplon (**1**) and its regioisomer **4**.



and therefore we decided to synthesize these and other potential impurities as standards.

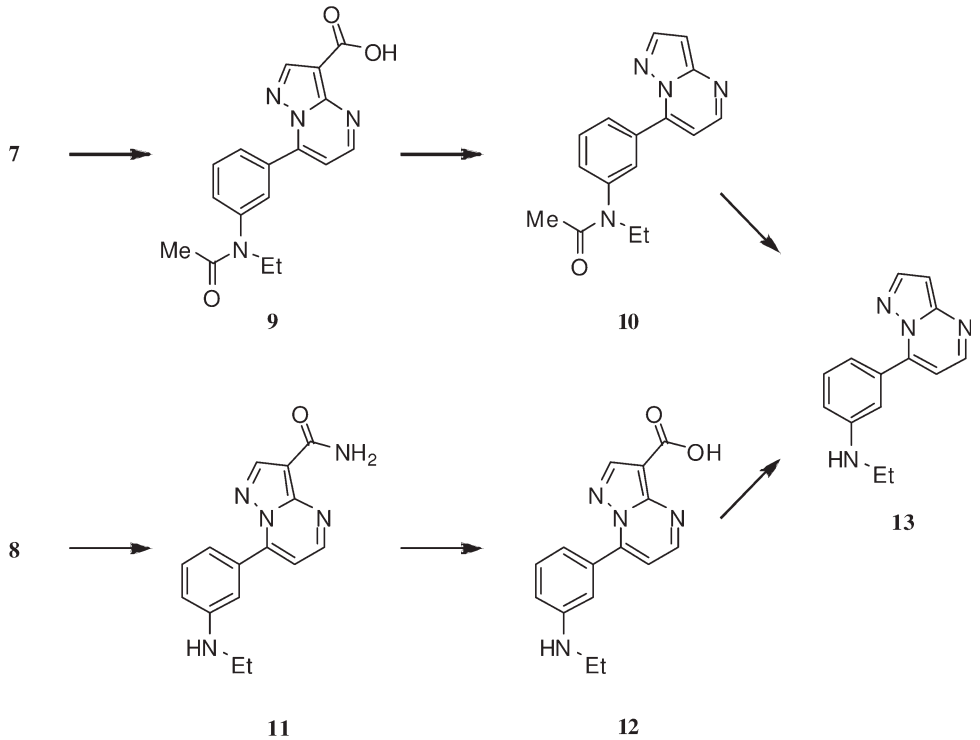


From the structures, it is evident that compounds **5** and **6** are process-related impurities formed by reaction of the corresponding impurities in **2** with **3a**. On the other hand, compounds **7** and **8** are products of hydrolysis of zaleplon leading to the nitrile group hydrolysis and anilide group hydrolysis, respectively. Our initial stress tests of zaleplon envisaged also formation of other similar impurities, as shown in Scheme 2, and therefore we decided to synthesise them.

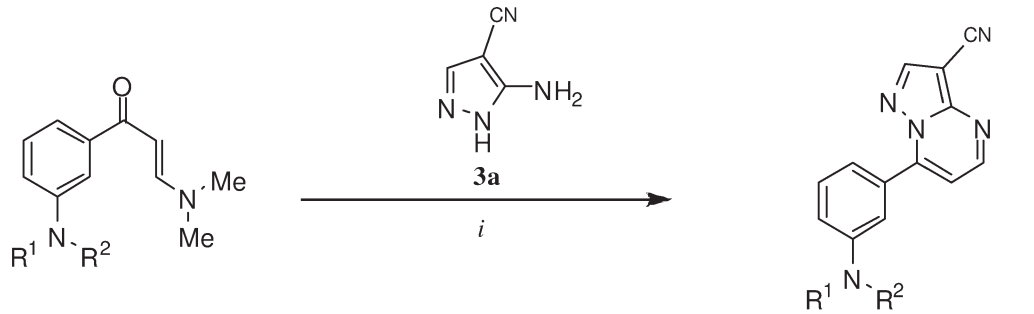
RESULTS AND DISCUSSION

During our development of generic zaleplon, we decided to prepare compounds **5–13** as standards. Compounds **5** and **6** were prepared analogously as zaleplon starting from commercially available compound **2b** and compound **2c**, respectively. Compound **2c** was prepared

Scheme 2. Possible degradation pathways of zaleplon under stress tests conditions.



Scheme 3. Preparation of process-related impurities **5** and **6** and impurity **8**.



2b R^1 = Ac, R^2 = H
2c R^1 = Ac, R^2 = Me
2d R^1 = CHO, R^2 = H
2e R^1 = CHO, R^2 = Et

i; HCl, EtOH, reflux

5 R^1 = Ac, R^2 = H
6 R^1 = Ac, R^2 = Me
8 R^1 = H, R^2 = Et
14 R^1 = CHO, R^2 = Et

from **2b** using sodium hydride/iodomethane. For the synthesis of compounds **8**, **11**–**13**, we decided to start from **2d** (R^1 = CHO, R^2 = H), which was easily obtained from 3-aminoacetophenone by subsequent formylation, folowed by treatment with DMFDMA. Compound **2d** then provided **2e** using NaH/DMF and EtI.

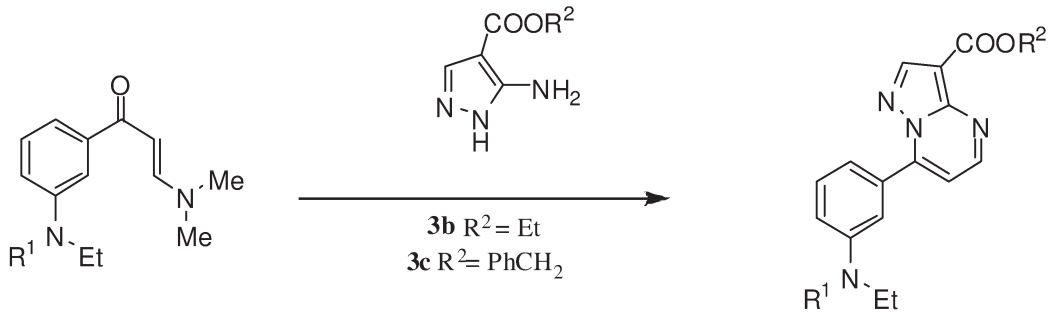
^{1}H NMR spectra of all of the compounds **2** showed that the methyl groups are nonequivalent as a result of the hindered rotation of dimethylamino group.

Compounds **2b** and **2c** heated with pyrazole **3a** in EtOH or MeOH and small amounts of concentrated hydrochloric acid provided good yields of the corresponding products **5** and **6**. Formyl derivative **2e** under the same conditions, was completely deprotected to give compound **8**. When the reaction was done with anhydrous solution of HCl in EtOH or in formic acid, the corresponding formyl derivative **14** was obtained (Scheme 3).

We intended to prepare amide impurity **7** by aminolysis of the corresponding ethyl ester and we also hoped that hydrolysis of this ester can provide acid **9**. For this purpose we prepared pyrazolecarboxylate **3b** using a modification of the literature procedure [11]. Similarly, also the corresponding benzyl ester **3c** was prepared [12]. Using general procedure described above, starting from compounds **2a** and **2e**, esters **15-18** were prepared (Scheme 4).

Aminolysis of both esters **15** and **16** to the corresponding amides **19** and **20** was very sluggish even using saturated ethanolic ammonia at 100°C under pressure; the mixtures after five days still contain about 10% of the starting compounds. Compound **19** was also

Scheme 4. Preparation of esters **15–18**.

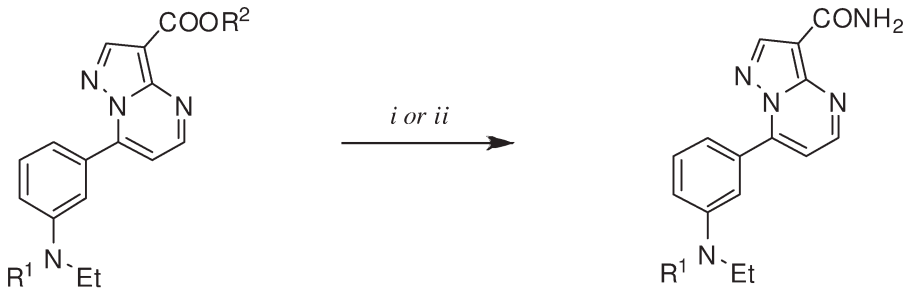


2a R^1 = Ac
2e R^1 = CHO

i; HCl, EtOH, reflux

15 R^1 = Ac, R^2 = Et
16 R^1 = H, R^2 = Et
17 R^1 = Ac, R^2 = $PhCH_2$
18 R^1 = H R^2 = $PhCH_2$

Scheme 5. Aminolysis of esters **15** and **16**.



15 R^1 = Ac, R^2 = Et
16 R^1 = H, R^2 = Et

19 R^1 = Ac
20 R^1 = H

i; NH_3, EtOH, 100 °C, 5 d; *ii,* NH_3, EtOH, $MgBr_2$, 100 °C, 1 d

obtained using catalysis [13] with $MgBr_2$, which shortened the reaction time but the crude mixture contained several impurities not present in case the reaction was done without the catalyst (Scheme 5).

Our initial attempts to synthesize acid **9** by hydrolysis of the corresponding ester **15** led under all conditions used to complex mixtures. Therefore the benzyl esters **17** and **18** were prepared and their hydrogenolytic debenzylation provided the corresponding acids **9** and **12** (Scheme 6). However, prolongation of the reaction time led to partial overreduction providing compounds having molecular weight higher by 4H (LC-MS).

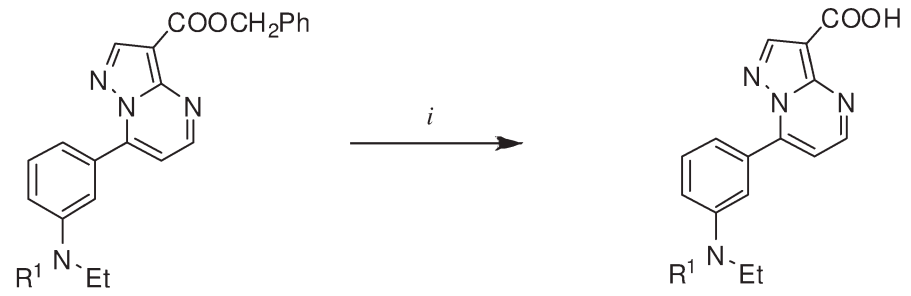
Initially we tried to avoid direct condensation of compounds **2a** and **2e** with 3-amino-4-pyrazol carboxylic acid (**3d**) and its amide (**3e**) since we expected partial hydrolysis and decarboxylation during the reaction. When we tried to do the reaction of **2a** with **3d** in a mixture of ethanol and hydrochloric acid, a mixture of the required acid **9** and its ethyl ester **15** was formed. However, we found that at 50°C in acetic acid the reaction is clean to give the required product **9** in good yield. Similarly, using formic acid and the following hydrolysis with aqueous hydrochloric acid, unsubstituted compound **12** was obtained (Scheme 7).

EXPERIMENTAL

Reagents used in the synthesis were purchased from Sigma-Aldrich and were used without purification.

Melting points were measured on a Kofler block and are uncorrected. The IR spectra were measured on a Nicolet Nexus FTIR instrument (Thermo) by accumulation of 64 scans with 4 cm^{-1} resolution using the ATR technique (ZnSe crystal); wavenumbers are given in cm^{-1}. The UV spectra were recorded on a Hewlett-Packard 8452A spectrophotometer (ethanol) in the range 190–400 nm. NMR experiments were carried out on a Bruker Avance 250. The Mass spectra [MS/MS; ionization mode APCI(+)] were measured on an API 3000 PE machine (Sciex Instruments, Applied Biosystems).

Scheme 6. Debenzylation of benzyl esters **17** and **18**.

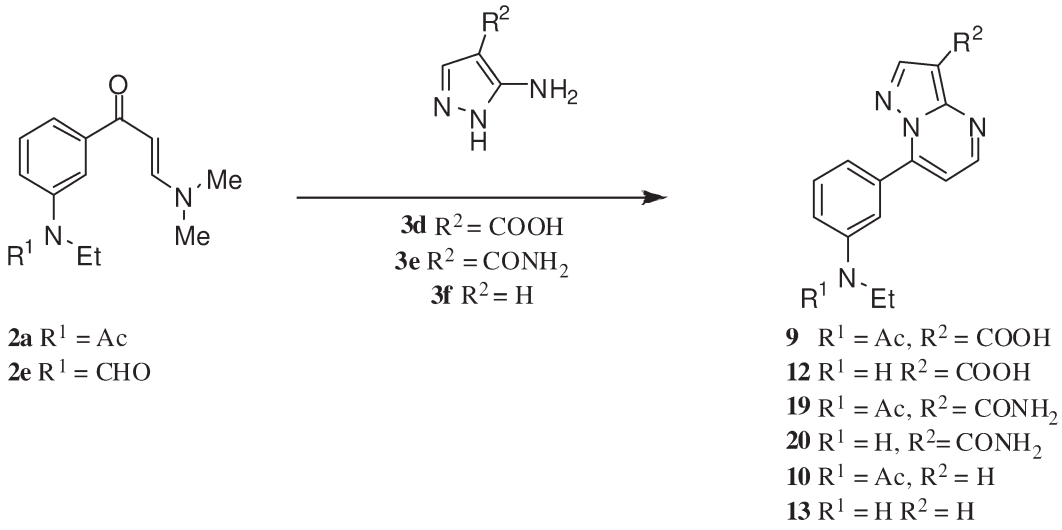


17 R^1 = Ac
18 R^1 = H

9 R^1 = Ac
12 R^1 = H

i; H_2, EtOH, Pd/C

Scheme 7. Preparation of amides and acids by direct condensation.



2a R^1 = Ac
2e R^1 = CHO

9 R^1 = Ac, R^2 = COOH
12 R^1 = H R^2 = COOH
19 R^1 = Ac, R^2 = $CONH_2$
20 R^1 = H, R^2 = $CONH_2$
10 R^1 = Ac, R^2 = H
13 R^1 = H R^2 = H

The purity of the prepared substances was evaluated by TLC on silica gel (FP KG F 254, Merck). Flash chromatography was performed on silica gel Merck, particle size 0.04–0.063 mm. Centrifugally accelerated axial chromatography was done using Cyclograph™ instrument (Analtech) with silica gel prescraped rotors.

***N*-[3-[(2*E*)-3-(Dimethylamino)prop-2-enoyl]phenyl]-*N*-methylacetamide (2c).** *N*-[3-[(2*E*)-(3-(Dimethylamino)prop-2-enoyl]phenyl]acetamide (**2b**, 5.8 g, 25 mmol) was added to a stirred 50% suspension of NaH (1.5 g) in DMF (80 mL) and the mixture was stirred under nitrogen for 1 h. Then a solution of iodomethane (5 g, 35 mmol) in DMF (10 mL) was added dropwise to the mixture and stirred at ambient temperature for 2.5 hrs. The mixture was poured into water (300 mL), washed with hexane and then the aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL, 5 × 20 mL). The extract was washed with brine and dried with $MgSO_4$. Crystallization of the residue after evaporation from ethyl acetate provided 5.2 g of yellow crystals (91%), mp 140–144°C. IR: CH 2815, C=O 1637, C=C 1585, 1538, CH 1367 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.89 (s, 3H, CH_3CO), 2.88 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 3.29 (s, 3H, NCH_3), 5.65 (d, J = 12.5, 1H, =CHCO), 7.26-7.87 (m, 5H, Ar—H, =CH—N); ^{13}C NMR ($CDCl_3$): 22.45, 37.10, 45.15, 91.66, 126.07, 126.62, 129.29, 129.43, 142.32, 144.56, 154.65, 170.46, 186.96. Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C 68.27; H 7.37; N 11.37. Found: C 68.22; H 6.94; N 11.06. HRMS Calcd. for $C_{14}H_{19}N_2O_2$ $(M+H)^+$ 247.14465. Found: 247.14406.

***N*-(3-Acetylphenyl)formamide.** A mixture of 3-aminoacetophenone (10 g, 0.07 mol) and formic acid (100 mL) was refluxed for 10 hrs. Residue after evaporation was then crystallized from toluene (charcoal) to provide 10.5 g of beige crystals (87%); mp 92–94°C [ref. 14 mp 93–94°C (Et_2O)]. IR: NH 3256, 3194, 3139, CH 3076, 3021, C=O 1667, C=C 1591, 1556, 1477 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.61 (s, 3H, CH_3), 7.27-8.07 (m, 4H, Ar—H), 8.44 (s, 1H, CHO). Anal. Calcd. for $C_9H_9NO_2$: C 66.25; H 5.56; N 12.06. Found: C 66.38; H 5.78; N 12.34. HRMS Calcd. for $C_9H_{10}NO_2$ $(M+H)^+$ 164.07116. Found: 164.07104.

***N*-[3-[(2*E*)-3-(Dimethylamino)prop-2-enoyl]phenyl]formamide (2d).** A solution of *N*-(3-acetylphenyl)formamide (3.25 g, 20 mmol) and DMFDMA (4.5 g, 37.8 mmol) in DMF (8 mL) was refluxed for 8 hrs and then stirred overnight. The formed yellow crystals were filtered off; yield 2.5 g (66%), mp 162–165°C. IR: NH 3229, 3184, CH 3066, 2846, 2767, C=O 1698, 1636, C=C 1595, 1516 cm^{-1}. ^1H NMR ($DMSO_{d6}$): δ 2.91 (s, 3H, NCH_3), 3.14 (s, 3H, NCH_3), 5.73 (d, 1H, J = 12.5, [dnond]CHCO), 7.37-8.01 (m, 5H, Ar—H, =CH—N), 8,30 (s, 1H, CHO), 10.23 (bs, 1H, NH). Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C 66.04; H 6.47; N 12.84. Found: C 66.21; H 6.67; N 13.01. HRMS Calcd. for $C_{12}H_{15}N_2O_2$ $(M+H)^+$ 219.11335. Found: 219.11310.

***N*-[3-[(2*E*)-3-(Dimethylamino)prop-2-enoyl]phenyl]-*N*-ethylformamide (2e).** Compound **2d** (2.52 g, 11.6 mmol) was added to a stirred 50% suspension of NaH (0.7 g, 14.6 mmol) in DMF (40 mL), and the mixture was stirred under nitrogen for 1 h. The mixture was cooled with ice-water and a solution of iodoethane (2.3 g, 15 mmol) in DMF (5 mL) was added dropwise and stirred at ambient temperature for 4 hrs. After that the mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with brine and dried with $MgSO_4$. Crystallization of the residue after evaporation from ethyl acetate provided 0.63 g of yellow crystals (22%), mp 69–73°C. IR: CH 2922, 2809, C=O 1667, 1634, C=C 1548, 1482 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.17 (t, 3H, J = 7.2, CH_3), 2.96 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 3.85 (q, 2H, J = 7.2, NCH_2), 5.71 (d, 1H, J = 12.3, =CHCO), 7.23-7.86 (m, 5H, Ar—H, =CH—N), 8.38 (s, 1H, CHO). Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C 68.27; H 7.37; N 11.37. Found: C 68.21; H 7.52; N 11.51. HRMS Calcd. for $C_{14}H_{19}N_2O_2$ $(M+H)^+$ 247.14465. Found: 247.14392.

General procedure for the synthesis of compounds 5, 6, 15, 17. Typically, a mixture of 3-(dimethylamino)-1-phenylprop-2-en-1-one **2** (10 mmol) and pyrazole **3** (10 mmol), ethanol (50 mL) and hydrochloric acid (1 mL) was refluxed for 1 h. The mixture was cooled down, the formed precipitate was filtered off to give the crude product, which was then crystallized from an appropriate solvent.

N-*[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]acetamide (5).* This compound was obtained after crystallization from *i*-PrOH in 77% yield according to the above general procedure; mp 257–261°C (ref. 15 mp 254–255°C). IR: NH 3314, CH 3092, CN 2235, C=O 1687, C=C + C=N 1615, 1583, 1538, 1478 cm^{-1}. UV λ_{max} (log ε): 204 (4.30), 234 (4.60), 338 (3.91). ^1H NMR ($CDCl_3$): δ 2.09 (s, 3H, CH_3CO), 7.50-8.34 (m, 5H, Ar—H), 8.86 (s, 1H, H-2), 8.90 (d, 1H, J = 5.0, H-5), 10.23 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$): 23.94, 81.34, 110.62, 113.37, 119.89, 122.01, 124.27, 129.05, 129.82, 139.41, 147.20, 147.51, 151.05, 153.71, 168.65. Anal. Calcd. for $C_{15}H_{11}N_5O$: C 64.97; H 4.00; N 25.26. Found: C 65.22; H 3.94; N 12.26. HRMS Calcd. for $C_{15}H_{12}N_5O$ $(M+H)^+$ 278.10419. Found: 278.10364.

N-*[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]*-N-*methylacetamide (6).* This compound was obtained after crystallization from *i*-PrOH in 60% yield according to the above general procedure; mp 202–205°C. IR: CH 3075, C≡N 2231, C=O 1645, C=C + C=N 1613, 1549, 1479 cm^{-1}. UV λ_{max} (log ε): 204 (4.40), 232 (4.58), 338 (3.85). ^1H NMR ($CDCl_3$): δ 2.01 (s, 3H, CH_3CO), 3.36 (s, 3H, CH_3N), 7.21-7.51 (m, 2H, Ar—H), 7.68 (t, 1H, J = 10.0, H-14), 7.94-7.99 (m, 2H, Ar—H), 8.44 (s, 1H, H-2), 8.81 (d, 1H, J = 5.0, H-5). ^{13}C NMR ($CDCl_3$): 22.63, 35.76, 83.73, 109.87, 112.51, 128.41, 129.57, 130.35, 131.03, 131.65, 143.47, 146.94, 147.11, 151.32, 152.61, 169.63. Anal. Calcd. for $C_{16}H_{13}N_5O$: C 65.97; H 4.50; N 24.04. Found: C 66.12; H 4.65; N 24.36. HRMS Calcd. for $C_{16}H_{14}N_5O$ $(M+H)^+$ 292.11983. Found: 292.11948.

Ethyl 7-[3-[acetyl(ethyl)amino]phenyl]pyrazolo[1,5-a]pyrimidin-3-carboxylate (15). This compound was obtained after crystallization from EtOH in 93% yield according to the above general procedure; mp 127–132°C. IR: OH 3390, CH 2971, C=O 1688, 1651, C=C + C=N 1602, 1547, 1489 cm^{-1}. UV λ_{max} (log ε): 206 (4.36), 234 (4.42), 340 (3.79). ^1H NMR ($CDCl_3$): δ 1.18 (t, 3H, J = 7.1, $NCH_2C\mathbf{H}_3$), 1.41 (t, 3H, J = 7.1, $OCH_2C\mathbf{H}_3$), 1.95 (s, 3H, CH_3CO), 3.81 (q, 2H, J = 7.1, NCH_2), 4.45 (q, 2H, J = 7.1, OCH_2), 7.14 (d, 1H, J = 2.7, H-6), 7.29-8.01 (m, 4H, Ar—H), 8.61 (s, 1H, H-2), 8.89 (d, 1H, J = 2.7, H-5). ^{13}C NMR ($CDCl_3$): 13.11, 14.51, 23.00, 44.09, 60.47, 103.33, 109.11, 128.72, 129.60, 130.20, 131.11, 131.67, 143.30, 146.48, 147.41, 148.91, 152.44, 162.47, 169.87. Anal. Calcd. for $C_{19}H_{20}N_4O_3$: C 64.76; H 5.72; N 15.90. Found: C 64.36; H 5.93; N 16.17. HRMS Calcd. for $C_{19}H_{21}N_4O_3$ $(M+H)^+$ 353.16137. Found: 353.16077.

Benzyl 7-(3-(N-ethylacetamido)phenyl)pyrazolo[1,5-a]pyrimidin-3-carboxylate (17). This compound was obtained after flash chromatography (hexane–acetone 6 : 4) and following crystallization from EtOH in 62% yield according to the above general procedure (reaction time 4 hrs); mp 112–114°C. IR: CH 2968, 2930, C=O 1694, 1652, C=C + C=N 1610, 1545, 1480. UV λ_{max} (log ε): 206 (4.54), 234 (4.52), 340 (3.95). ^1H NMR ($CDCl_3$): δ 1.17 (t, 3H, J = 7.2, CH_3), 1.94 (s, 3H, CH_3CO), 3.82 (q, 2H, J = 7.2, NCH_2), 5.46 (s, 2H, OCH_2), 7.12-8.00 (m, 10H, Ar—H), 8.62 (s, 1H, H-2), 8.82 (d, 1H, J = 5.0, H-5). ^{13}C NMR ($CDCl_3$): 13.12, 22.99, 44.07, 65.94, 103.08, 109.12, 128.05, 128.18, 128.50, 128.67, 129.61, 130.19, 131.12, 131.66, 136.42, 143.38, 146.47, 147.47, 149.15, 152.37, 162.10, 169.75. Anal. Calcd. for $C_{24}H_{22}N_4O_3$: C 69.55; H 5.35; N 13.52. Found: C 69.44; H 5.39; N 11.67. HRMS Calcd. for $C_{24}H_{23}N_4O_3$ $(M+H)^+$ 415.17702. Found: 415.17682.

***N*-[3-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)phenyl]-*N*-ethylformamide (14).** A mixture of **2e** (0.62 g, 2.5 mmol) and pyrazole **3a** (0.3 g, 2.7 mmol) was dissolved in ethanol (10 mL) and then a saturated solution of HCl in ethanol (1 mL) was added. The mixture was refluxed for 3–4 hrs, evaporated and the residue was crystallized from MeOH provided 0.45 g (62%) of yellow crystals; mp 125–128°C. IR: CH 3089, 2974, C≡N 2230, C=O 1678, C=C + C=N 1611, 1552, 1493 cm^{-1}. UV λ_{max} (log ε): 204 (4.41), 234 (4.63), 338 (3.89). ^1H NMR ($CDCl_3$): δ 1.24 (t, 3H, J = 7.5, CH_3), 3.95 (q, 2H, J = 7.5 CH_2), 7.14-8.65 (m, 8H, Ar—H, NCHO). ^{13}C NMR ($CDCl_3$): 13.09, 40.15, 83.51, 109.90, 111.09, 112.48, 124.83, 126.98, 127.46, 130.36, 131.01, 141.54, 146.60, 147.17, 151.07, 152.60, 161.69. Anal. Calcd. for $C_{16}H_{13}N_5O$: C 65.97; H 4.50; N 24.04. Found: C 66.23; H 4.72; N 24.24. HRMS Calcd. for $C_{16}H_{14}N_5O$ $(M+H)^+$ 292.11984. Found: 292.11935.

General procedure for the synthesis of compounds 8, 16, 18, 10, 13. Typically, a mixture of 3-(dimethylamino)-1-phenylprop-2-en-1-one **2** (10 mmol), pyrazole **3** (10 mmol), ethanol (50 mL) and 10% hydrochloric acid (10 mL) was refluxed for 1 h. The mixture was evaporated, the residue was triturated with 10% Na_2CO_3, the insoluble portion was filtered off to give the crude product, which was then crystallized from an appropriate solvent.

7-[3-(Ethylamino)phenyl]pyrazolo[1,5-a]pyrimidin-3-carbonitrile (8). This compound was obtained after crystallization from EtOH in 95% yield according to the above general procedure; mp 172–179°C. IR: CH 3071, 2707, 2662, 2478, C≡N 2227, C=C + C—N 1612, 1544, 1495 cm^{-1}. UV λ_{max} (log ε): 206 (4.15), 234 (4.32), 338 (3.68). ^1H NMR (DMSO): δ 1.24 (t, 3H, J = 7.5, CH_3), 3.26 (q, 2H, J = 7.5, CH_2), 7.26-8.91 (m, 7H, Ar—H). ^{13}C NMR (DMSO): 12.75, 81.32, 110.65, 113.37, 129.60, 130.39, 147.20, 147.50, 151.05, 153.69. Anal. Calcd. for $C_{15}H_{13}N_5$: C 68.42; H 4.98; N 26.60. Found: C 68.18; H 4.73; N 26.86. HRMS Calcd. for $C_{15}H_{14}N_5$ $(M+H)^+$ 264.12492. Found: 264.12436.

Ethyl 7-[3-(ethylamino)phenyl]pyrazolo[1,5-a]pyrimidin-3-carboxylate (16). This compound was obtained after crystallization from EtOH in 84% yield according to the above general procedure; mp 189–202°C. IR: CH 3072, 2664, 2485, C=O 1705, C=C + C=N 1611, 1581, 1548, 1494 cm^{-1}. UV λ_{max} (log ε): 208 (4.31), 244 (4.44), 340 (3.84). ^1H NMR (DMSO): δ 1.25 (t, 3H, J = 7.2, $NCH_2C\mathbf{H}_3$), 1.33 (t, 3H, J = 7.2, $OCH_2C\mathbf{H}_3$), 3.29 (q, 2H, J = 7.5, NCH_2), 4.34 (q, 2H J = 7.2, OCH_2), 7.33-7.90 (m, 5H, Ar—H), 8.66 (s, 1H, H-2), 8.89 (d, 1H, J = 5.0, H-5). ^{13}C NMR (DMSO): 12.53, 14.40, 44.09, 59.55, 101.97, 109.88, 128.55, 129.61, 130.22, 130.98, 131.09, 131.76, 143.33, 146.68, 146.85, 148.16, 153.01, 161.69. Anal. Calcd. for $C_{17}H_{18}N_4O_2$: C 65.79; H 5.85; N 18.05. Found: C 65.47; H 6.04; N 18.25. HRMS Calcd. for $C_{17}H_{19}N_4O_2$ $(M+H)^+$ 311.15080. Found: 311.15021.

Benzyl 7-[3-(ethylamino)phenyl]pyrazolo[1,5-a]pyrimidin-3-carboxylate (18). This compound was obtained after flash chromatography (hexane–acetone 7 : 3 to hexane–acetone–methanol 7 : 3 : 1) followed by crystallization from EtOH in 60% yield according to the above general procedure; mp 145–157°C. IR: CH 3051, 2964, 2518, 2378, C=O 1695, C=C + C=N 1608, 1588, 1544, 1492 cm^{-1}. UV λ_{max} (log ε): 210 (4.35), 246 (4.46), 338 (3.88). ^1H NMR ($CDCl_3$): δ 1.47 (t, 3H, J = 7.2, CH_3), 3.50 (q, 2H, J = 7.5, NCH_2), 5.44 (s, 2H, OCH_2), 7.13-8.86 (m, 12H, Ar—H), 11.50 (bs, NH). ^{13}C NMR

($CDCl_3$): 11.00, 48.21, 66.01, 103.06, 109.51, 124.77, 126.43, 128.07, 128.14, 128.50, 130.44, 131.97, 135.93, 136.31, 145.58, 147.39, 148.99, 152.64, 162.13. Anal. Calcd. for $C_{22}H_{20}N_4O_2$: C 70.95; H 5.41; N 15.04. Found: C 70.68; H 5.33; N 15.22. HRMS Calcd. for $C_{22}H_{21}N_4O_2$ $(M+H)^+$ 373.16645. Found: 373.16605.

***N*-Ethyl-*N*-(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)acetamide (10).** This compound was obtained after crystallization from EtOH in 72% yield according to the above general procedure; mp 105–108°C. IR: CH 3051, 2973, C=O 1646, C=C + C=N 1600, 1537, 1393 cm^{-1}. UV λ_{max} (log ε): 204 (4.33), 234 (4.61), 350 (3.55). ^1H NMR (DMSO): δ 1.04 (t, 3H, J = 7.1, CH_3), 1.82 (s, 3H, CH_3CO), 3.70 (q, 2H, J =7.1, NCH_2), 6.84 (d, 1H, J = 2.2, H-3), 7.31 (d, 1H, J = 4.3, H-6), 7.53 (d, 1H, J = 7.9, H-4′ or H-6′), 7.67 (t, 1H, J = 7.9, H-5′), 8.07 (m, 1H, H-2′), 8.13 (d, 1H, J = 7.9, H-4′ or H-6′), 8.27 (d, 1H, J = 2.2, H-2), 8.62 (d, 1H, J = 4.3, H-5). ^{13}C NMR (DMSO): 12.90, 22.64, 43.07, 96.61, 107.85, 129.16, 129.67, 130.61, 131.79, 142.56, 144.46, 144.50, 149.34, 149.48, 170.03. Anal. Calcd. for $C_{16}H_{16}N_4O$: C 68.55; H 5.75; N 19.99. Found: C 68.46; H 5.90; N 20.16. HRMS Calcd. for $C_{16}H_{17}N_4O$ $(M+H)^+$ 281.14024. Found: 281.13962.

N-*Ethyl*-N-*(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)amine (13). This compound was obtained after crystallization from EtOH in 66% yield according to the above general procedure; mp 185–190°C. IR: CH 3062, 2913, 2661, 2483, C=C + C=N 1606, 1580, 1538, 1452 cm^{-1}. UV λ_{max} (log ε): 204 (4.08), 232 (4.53), 352 (3.62). ^1H NMR (DMSO): δ 1.27 (t, 3H, J = 7.2, CH_3), 3.37 (q, 2H, J = 7.2, CH_2), 6.85 (d, 1H, J = 2.4, H-3), 7.25 (d, 1H, J = 4.4, H-6), 7.46 (d, 1H, J = 7.3, H-4′ or H-6′), 7.61 (t, 1H, J = 7.9, H-5′), 7.85 (d, 1H, J = 7.3, H-4′ or H-6′), 7.97 (m, 1H, H-2′), 8,28 (d, 1H, J = 2.4, H-2), 8.64 (d, 1H, J = 4.4, H-5), 11.75 (bs, NH). ^{13}C NMR (DMSO): 12.07, 42.96, 96.60, 107.75, 128.33, 129.24, 129.70, 130.33, 131.72, 142.72, 144.50, 144.94, 149.30, 149.54. Anal. Calcd. for $C_{14}H_{14}N_4$: C 70.57; H 5.92; N 23.51. Found: C 70.21; H 5.66; N 23.04. HRMS Calcd. for $C_{14}H_{15}N_4$ $(M+H)^+$ 239.12967. Found: 239.12918.

7-(3-(*N*-Ethylacetamido)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (19).

Method A. A mixture of compound **15** (1 g, 2.8 mmol) and ethanol saturated with ammonia (10 mL) was heated in a pressure tube at 100°C for 5 days (TLC; toluene–ethanol–dioxane–ammonia 5 : 2 : 4 : 1). The residue after evaporation was purified by flash chromatography (hexane–acetone, 7 : 3) to give 0.65 g of crude compound **19** and its crystallization (EtOH) provided 0.45 g (50%) of yellowish crystals; mp 233–237°C. IR: NH 3394, 3121, CH 2984, C=O 1652, C=C + C=N 1622, 1597, 1544, 1482 cm^{-1}. UV λ_{max} (log ε): 206 (4.49), 234 (4.51), 350 (3.82). ^1H NMR (DMSO): δ 1.06 (t, 3H, J = 7.2, $NCH_2C\mathbf{H}_3$), 1.85 (s, 3H, $C\mathbf{H}_3CO$), 3.72 (q, 2H, J = 7.2, CH_2), 7.54-8.20 (m, 7H, 5 × Ar—H, 1 × $CONH_2$), 8.61 (s, 1H, H-2), 8.86 (d, 1H, J = 4.5, H-5). ^{13}C NMR (DMSO): 12.91, 22.67, 43.37, 105.49, 109.32, 128.81, 129.43, 129.75, 130.11, 131.12, 142.63, 145.73, 146.09, 147.53, 151.86, 162.54, 169.70. UV λ_{max} (log ε): 206 (4.49), 234 (4.51), 350 (3.82). Anal. Calcd. for $C_{17}H_{17}N_5O_2$: C 63.15; H 5.30; N 21.66. Found: C 63.38; H 5.48; N 21.99. HRMS Calcd. for $C_{17}H_{18}N_5O_2$ $(M+H)^+$ 324.14605. Found: 324.14551.

Method B. The procedure is similar as Method (A), only 0.2 g of $MgBr_2$ was added and the mixture was heated for 1 day to provide after chromatography 38% of **19**.

Method C. A mixture of **2a** (0.2 g, 0.8 mmol), 3-amino-4-pyrazol carboxamide (**3e**; 0.1 g, 0.8 mmol), and ethanol (3.8 mL) with concentrated HCl (0. 1 mL) was heated in a vial at 50°C for 24 hrs. A solid precipitated during the heating. The mixture was cooled down, the precipitate was filtered off to give 0.17 g of yellow crystals (66%); mp 233–237°C.

7-[3-(Ethylamino)phenyl]pyrazolo[1,5-*a*]pyrimidin-3-carboxamide (20). Using Method A described for the preparation of 7-[3-[acetyl(ethyl)amino]phenyl]pyrazolo[1,5-*a*]pyrimidin-3-carboxamide (**19**), compound **20** was obtained in 60% yield; mp 193–203°C. IR: NH 3366, 3305, 3116, CH 2950, C=O 1666, C=C + C=N 1626, 1543, 1513, 1472 cm^{-1}. UV λ_{max} (log ε): 206 (4.07), 246 (4.15), 350 (3.81). ^1H NMR (DMSO): δ 1.20 (t, 3H, J = 7.1, CH_3), 3.10 (q, 2H, J = 7.1, CH_2), 5.90 (t, 1H, J = 5.3, NH), 6.80-7.38 (m, 5H, Ar—H), 7.50 (s, 1H, $CONH_2$), 7.63 (s, 1H, $CONH_2$), 8.59 (s, 1H, H-2), 8.81 (d, 1H, J = 4.5, H-5). ^{13}C NMR (DMSO): 14.21, 37.22, 105.17, 108.77, 112.55, 114.79, 116.61, 129.06, 130.45, 145.60, 146.80, 148.18, 148.88, 151.77, 162.64. Anal. Calcd. for $C_{15}H_{15}N_5O$: C 64.04; H 5.37; N 24.90. Found: C 63.87; H 5.22; N 25.34. HRMS Calcd. for $C_{15}H_{16}N_5O$ $(M+H)^+$ 282.13549. Found: 282.13510.

7-(3-(*N*-Ethylacetamido)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (9). A mixture of *N*-[(2*E*)-3-[3-(dimethylamino)prop-2-enoyl]phenyl]-*N*-ethylacetamide (**2a**, 1 g, 4 mmol), 3-amino-4-pyrazolecarboxylic acid (**3d**; 0.5 g, 4 mmol), acetic acid (20 mL) was stirred at 50°C for 24 hrs. The mixture was evaporated, the residue was dissolved in CH_2Cl_2 and extracted with 10% solution of Na_2CO_3 (5 × 8 mL). Insoluble particles were filtered off from the collected aqueous portions and the clear solution was acidified with acetic acid. Then the solution was extracted with CH_2Cl_2 (10 × 15 mL) and the extract was dried with $MgSO_4$. The residue after evaporation was triturated with water and the insoluble portion was filtered off to give 0.3 g (48%); mp 195–200°C (decomp.). IR: NH 3293, CH 2973, 2934, C=O 1652, 1575, 1544, C=C + C=N 1402, CO 1299 cm^{-1}. UV λ_{max} (log ε): 206 (4.11), 236 (4.33), 352 (3.56). ^1H NMR (250 MHz, DMSO): 1.05 (t, 3H, J = 7.1, $NCH_2C\mathbf{H}_3$), 2.08 (s, 3H, $COCH_3$), 3.72 (q, 2H, J = 7.1, CH_2), 7.31 (d, 1H, J = 4.4, H-6), 7.54 (d, 1H, J = 7.6, H-4′ or H-6′), 7.67 (d, 1H, J = 7.6, H-5′), 8.01 (m, 1H, H-2′), 8.11 (d, 1H, J = 7.6, H-4′ or H-6′), 8.34 (s, 1H, H-2), 8.65 (d, 1H, J = 4.4, H-5). ^{13}C NMR (DMSO): 12.93, 22.65, 43.55, 107.78, 111.84, 128.59, 129.17, 129.67, 130.67, 131.81, 142.60, 145.00, 146.92, 147.06, 150.34, 165.72, 174.69. HRMS Calcd. for $C_{17}H_{17}N_4O_3$ $(M+H)^+$ 325.13007. Found: 325.129469.

7-(3-(*N*-Ethylamino)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (12). A mixture of *N*-[(2*E*)-3-[3-(dimethylamino)prop-2-enoyl]phenyl]-*N*-ethylformamide (**2a**) (**2e,** 0.25 g, 1 mmol), 3-amino-4-pyrazolecarboxylic acid (**3d**; 0.13 g, 1 mmol), formic acid (4 mL) was stirred at 75°C for 16 hrs. The mixture was evaporated and the residue was stirred with concentrated hydrochloric acid (3 mL) at 50°C for 15 min. The residue after evaporation was dissolved in water (10 mL), alkalized with 10% NaOH and extracted with diethyl ether (2 × 5 mL). The extract was dried with $MgSO_4$ and the residue after evaporation containing according to TLC pure product of decarboxylation **13** (50 mg, 21%). The aqueous layer was neutralized with acetic acid and extracted with dichloromethane (3 × 10 mL). The extract was washed with water and dried with $MgSO_4$. The residue after evaporation was triturated with water and the insoluble

portion was filtered off to provide 0.19 g (64%) of yellowish crystals; mp 198–206°C (decomp.). IR: CH 2981, 2941, C=O 1667, 1652, NH 1538, CO 1231 cm^{-1}. UV λ_{max} (log ε): 204 (4.35), 236 (4.43), 352 (3.40). ^{1}H NMR (250 MHz, DMSO): 1.18 (t, 3H, $J = 7.2$, $NCH_2C\mathbf{H}_3$), 3.07 (q, 2H, $J = 7.2$, CH_2), 6.78 (d, 1H, $J = 4.4$, H-6), 7.14-7.35 (m, 4H, arom. H), 8.57 (s, 1H, H-2), 8.78 (d, 1H, $J = 4.4$, H-5). ^{13}C NMR (DMSO): 14.23, 37.99, 109.22, 112.57, 114.69, 114.97, 116.62, 129.02, 130.17, 130.61, 147.01, 147.97, 152.40, 163.23, 173.05. HRMS Calcd. for $C_{15}H_{14}N_4O_3$ $(M+H)^+$ 298.106590. Found: 298.11893.

Acknowledgments. This work was a part of the Diploma work of Michaela Blahovcová, which was supported by Zentiva Prague.

REFERENCES AND NOTES

[1] Anon. Drugs Future 1996, 21, 37.

[2] Doplet, M.; Plosker, G. L. Drugs,2000, 60, 413.

[3] Walsh, J. K.; Pollak, C. P.; Scharf, M. B.; Schweitzer, P. K.; Vogel, G. W. Clin Neuropharmacol 2000, 23, 17.

[4] Dusza, J. P.; Tomcufcik, A. S.; Albright, J. D.; (American Cyanamide), US 4,626,538 (1985); Chem Abstr 1986, 105, 72777.

[5] Thurajrajan, P.; (American Cyanamide), US 5,714,607 (1995); Chem Abstr 1998, 128, 154095.

[6] Korycinska, M.; Stawinski, T.; Wieczorek, M.; (Adamed), WO 95,456 (2003); Chem Abstr 2003, 139, 381506.

[7] Korodi, F.; Fehér, E.; Magyar, E.; (TEVA Pharmaceuticals), WO 100828 (2002); Chem Abstr 2002, 138, 24725.

[8] Rádl, S. (Zentiva), WO 37,824 (2004); Chem Abstr 2004, 143, 43894.

[9] Bharathi, C.; Prabahar, K. J.; Prasad, C. S.; Karavana, K. M.; Magesh, S.; Handa, V. K.; Nadala, R.; Naidu, A. J Pharm Biomed Anal 2007, 44, 101.

[10] Rádl, S.; Blahovcová, M.; Tkadlecová, M.; Havlíček, J. Heterocycles, to appear.

[11] Howe, R. K.; Bolluyt, S. C. J Org Chem 1969, 34, 1713.

[12] Cusack, N. J.; Shaw, G.; Litchfield, G. J. J Chem Soc C 1971, 1501.

[13] Guo, Z.; Dowdy, E. D.; Li, W.-S.; Polniaszek, R.; Delaney, E. Tetrahedron Lett 2001, 42, 1843.

[14] Zhang, M. Q.; Haemers, A.; Vanden Berghe, D.; Pattyn, S. R.; Bollaert, W.; Levshin, I. J Heterocycl Chem 1991, 28, 673.

[15] Shaikh, A. C.;Chen C. J Labelled Compd Radiopharm 2008, 51, 72.