Convenient selective synthesis of pyrano[2,3-*d*]pyrimidines

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A selective method for the synthesis of substituted and annulated pyrano[2,3-*d*]pyrimidines consisting in acylation of 2-amino-3-cyano-4*H*-pyrans with acetic anhydride has been developed. It was shown for the first time that acid catalysis is more efficient in this reaction, rather than base catalysis as it has been believed earlier.

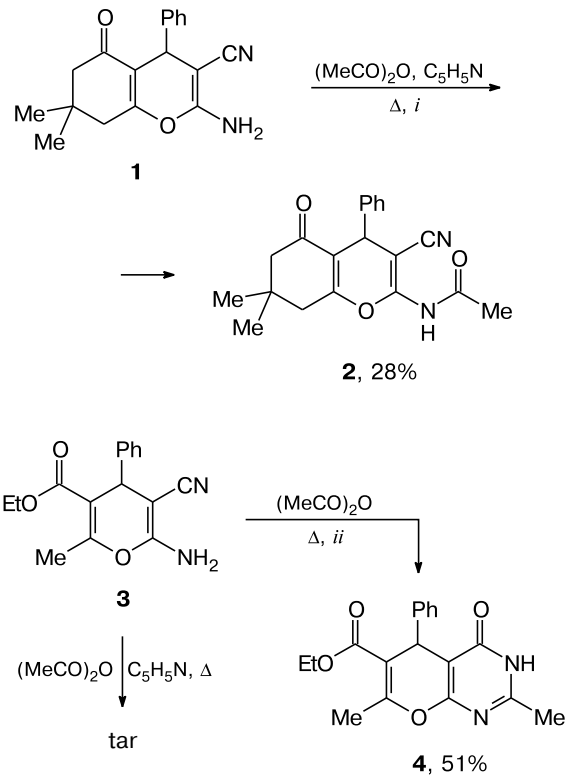
Key words: pyrano[2,3-*d*]pyrimidine, 2-amino-3-cyano-4*H*-pyrans annulated heterocycles, acylation, acid catalysis.

Heterocycles containing pyrano[2,3-*d*]pyrimidine fragment possess antibacterial and fungicide activity,[1—3] as well as are patented as the leucoforms of thermo-, tenso- and electrosensitive dyes.

One of the principal methods for the synthesis of substituted pyrano[2,3-*d*]pyrimidin-4-ones includes the reaction of acetic anhydride with substituted 2-amino-3-cyano-4*H*-pyrans with no catalyst or in the presence of basic catalysts (e.g., pyridine). However, this reaction is not always selective. Thus, the reaction of ethyl 2-amino-3-cyano-4,6-diphenyl-4*H*-pyran-5-carboxylate with acetic anhydride without a catalyst stops on the step of acylation of the amino group to afford ethyl 2-acetylamino-3-cyano-4,6-diphenyl-4*H*-pyran-5-carboxylate. Analogous reactivity of annulated 2-amino-3-cyano-4*H*-pyrans in the absence of a catalyst was observed earlier.

We decided to study the selectivity of this reaction. The reaction of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromen-3-carbonitrile (**1**) with acetic anhydride in the presence of pyridine afforded *N*-acetyl derivative **2** in low yield since the reaction is accompanied by strong resinification. On the contrary, the reaction of ethyl 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-carboxylate (**3**) with acetic anhydride under heating for 10 h in the absence of a catalyst led to ethyl 2,7-dimethyl-4-oxo-5-phenyl-3,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate (**4**), whereas the reaction in the presence of pyridine gave a tar-like mixture of products (TLC) (Scheme 1).

Scheme 1



i. 2 h; *ii*. 10 h.

Changing the reaction conditions and catalysts, we for the first time found that the reaction of acetic anhydride with 2-amino-4*H*-pyran-3-carbonitrile **3** in the presence of catalytic amounts (0.1 equiv.) of sulfuric acid proceeds with high selectivity to form substituted and annulated pyrano[2,3-*d*]pyrimidin-4-one **4**. At the same time, the yield increases to 67% and the reaction time considerably decreases: from 6—10 h in the absence of the catalyst to 5—10 min in the presence of the catalyst.

The reaction found by us is versatile and allows one to synthesize pyranopyrimidines **4—13** (Scheme 2) from various substituted and annulated 2-amino-4*H*-pyran-

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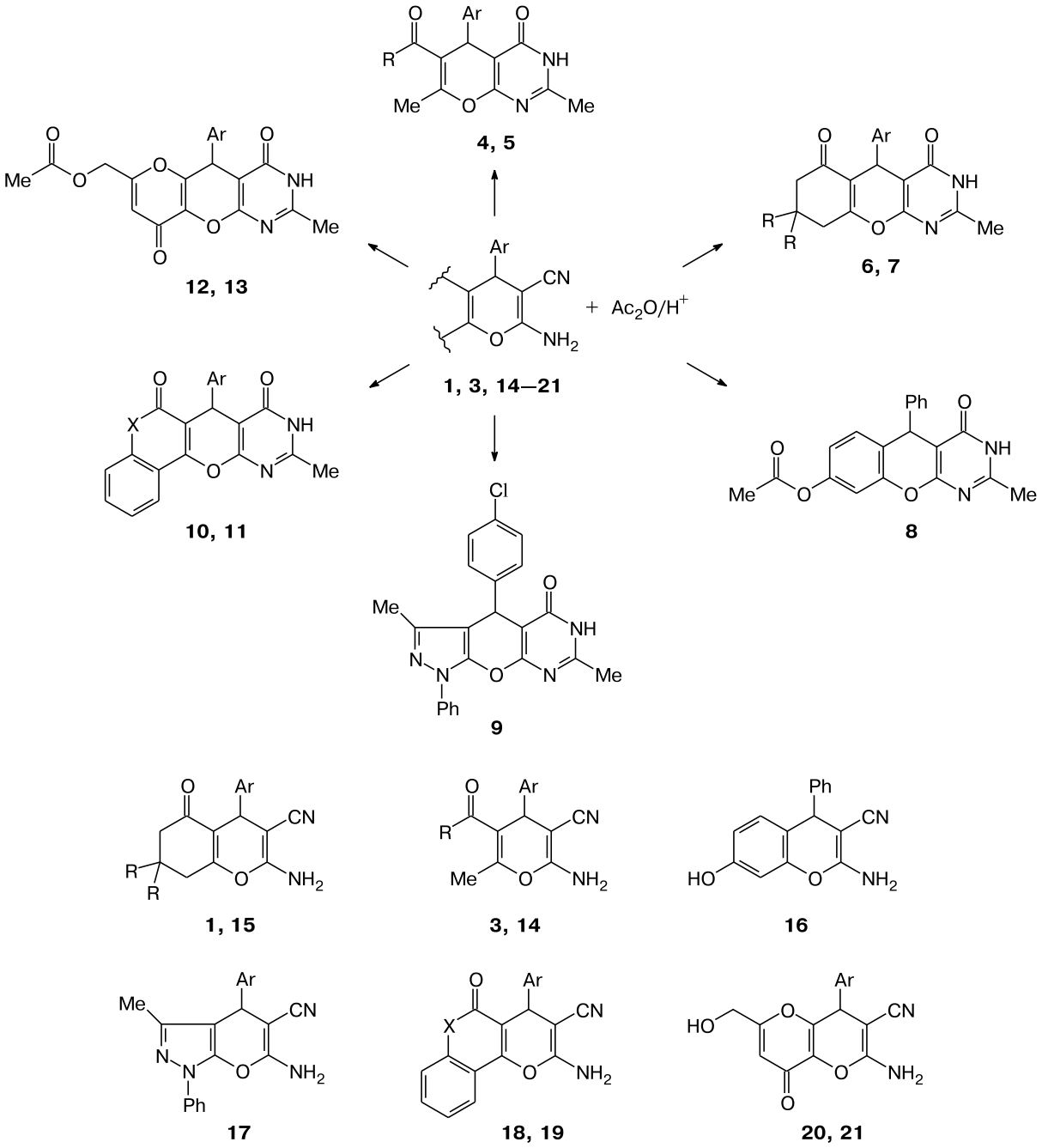
Scheme 2



1: R = Me, Ar = Ph
3: R = OEt, Ar = Ph
4: R = OEt, Ar = Ph
5: R = Me, Ar = 2-ClC_6H_4
6: R = Me, Ar = Ph
7: R = H, Ar = 2-C_4H_3S
10: X = O, Ar = Ph
11: X = S, Ar = 4-$MeOC_6H_4$
12: Ar = Ph
13: Ar = 4-ClC_6H_4
14: R = Me, Ar = 2-ClC_6H_4
15: R = H, Ar = 2-C_4H_3S
17: Ar = 4-ClC_6H_4
18: X = O, Ar = Ph
19: X = S, Ar = 4-$MeOC_6H_4$
20: Ar = Ph
21: Ar = 4-ClC_6H_4

3-carbonitriles **1**, **3**, **14—21**. All the pyrano[2,3-*d*]pyrimidines obtained, except **10**, have not been described in the literature.

If an OH group is present in the molecule of the starting pyran (compounds **16**, **20**, and **21**), it also undergoes acylation. The structures of compounds obtained were confirmed by the ^1H and ^{13}C NMR and IR spectroscopic data. In the IR spectra of compounds **4—12** synthesized, there is no absorption of a nitrile group, whereas a wide intensive absorption band in the region 3100—2700 cm^{-1}

is present, which corresponds to the stretching vibrations of the NH group of the pyrimidine fragment with strong hydrogen bonds. In the ^{1}H NMR spectra of compounds **4—13**, the signal for the 2-Me group as a singlet in the region 2.25—2.33 ppm and the signal for the proton of the pyran ring in the region 4.79—5.22 ppm are observed, as well as the signal for the NH group as a broad singlet in the region 12.40—12.70 ppm.

In conclusion, a simple and convenient selective method for the synthesis of pyrano[2,3-*d*]pyrimidin-4-ones consisting in the reaction of 2-amino-3-cyano-4*H*-pyrans with acetic anhydride in the presence of catalytic amounts of sulfuric acid has been developed.

Experimental

Melting points were measured on the Kofler apparatus. IR spectra were recorded on a Specord M82 spectrometer in KBr pellets (1 : 200). ^{1}H NMR spectra were recorded on a Bruker WM-250 and Bruker AM-300 spectrometers (250 and 300 MHz, respectively) in DMSO-d_6. ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer (50.32 MHz) in DMSO-d_6 (the JMODXH procedure).

The starting 2-amino-4*H*-pyrans **1**, **3**, **14—21** were obtained by the standard three-component procedure[9] from equimolar amounts of aromatic aldehyde, malononitrile and the corresponding nucleophilic agent (acetoacetic ester, acetylacetone, resorcinol, 3-methyl-1-phenylpyrazolin-5-one, 4-hydroxycoumarin, 4-hydroxythiocoumarin, kojic acid).

2-Acetylamino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (2). Pyridine (0.75 mL) was added to a solution of pyran **1** (0.98 g, 3 mmol) in acetic anhydride (2.5 mL) and the mixture was refluxed for 2 h (TLC-monitoring). Product **2** was isolated as a precipitate from the dark brown solution on cooling to 4 °C. The precipitate was washed with ethanol and light petroleum and recrystallized from ethanol. The yield was 0.28 g (28%), m.p. 228—230 °C. Found (%): C, 71.50; H, 6.05; N, 8.53. $C_{20}H_{20}N_2O_3$. Calculated (%): C, 71.41; H, 5.99; N, 8.33. IR (ν/cm^{-1}): 3160 (N—H); 2212 (C≡N), 1668 (amide-I), 1576 (amide-II). ^{1}H NMR, δ: 1.00, 1.09 (both s, 3 H each, C(7)—$(CH_3)_2$); 2.20 (s, 3 H, C$\underline{H}_3$—CO); 2.28 (AB-system, 2 H, C(8)H_2, J = 18.3 Hz); 2.67 (AB-system, 2 H, H_2C(6), J = 18.0 Hz); 5.49 (s, 1 H, H(4)); 7.33 (m, 5 H, C_6H_5); 11.45 (br.s, 1 H, NH). ^{13}C NMR, δ: 13.59, 18.00, 38.76 (overlap with the signal for DMSO), 57.26, 60.02, 107.18, 119.58, 126.68, 127.07, 128.30, 144.77, 156.47, 158.39, 165.34.

Pyrano[2,3-*d*]pyrimidines 4—13 (general procedure). 2-Amino-3-cyano-4*H*-pyran (5 mmol), acetic anhydride (5 mL), and concentrated sulfuric acid (0.5 mmol) were mixed. The reaction mixture obtained was refluxed for 10 min, cooled to room temperature and kept for 1 day. A precipitate formed was filtered off, washed with water (3×5 mL), ethanol (5 mL), and light petroleum (5 mL). The product obtained was recrystallized from ethanol and dried at 120 °C until the weight became constant.

Ethyl 2,7-dimethyl-4-oxo-5-phenyl-3,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate (4). The yield was 67%, m.p. 255—256 °C. Found (%): C, 66.05; H, 5.46; N, 8.62. $C_{18}H_{18}N_2O_4$. Calculated (%): C, 66.31; H, 5.52; N, 8.59. IR (ν/cm^{-1}): 3160—2700 (NH); 1712 (C=O). ^{1}H NMR, δ: 1.12 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 6.9 Hz); 2.25 (s, 3 H, C(2)CH_3); 2.40 (s, 3 H, C(7)CH_3); 4.03 (q, 2 H, CH$_3$C$\underline{H}_2$, J = 6.9 Hz); 4.79 (s, 1 H, H(5)); 7.22 (m, 5 H, C_6H_5); 12.49 (br.s, 1 H, NH). ^{13}C NMR, δ: 13.87, 18.41, 20.94, 35.87, 60.23, 100.62, 107.89, 126.64, 128.04, 128.10, 144.10, 158.21, 158.67, 159.93, 161.97, 165.64.

6-Acetyl-5-(2-chlorophenyl)-2,7-dimethyl-3,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidin-4(3*H*)-one (5). The yield was 55%, m.p. 235—237 °C. Found (%): C, 61.62; H, 4.48; N, 8.50. $C_{17}H_{15}ClN_2O_3$. Calculated (%): C, 61.73; H, 4.57; N, 8.47. IR (ν/cm^{-1}): 3080—2600 (NH); 1696 (C=O). ^{1}H NMR, δ: 2.18, 2.23, 2.25 (all s, 3 H each, C(2)CH_3, C(7)CH_3, C(=O)CH_3); 5.22 (s, 1 H, H(5)); 7.27 (m, 4 H, C_6H_4); 12.37 (br.s, 1 H, NH).

2,8,8-Trimethyl-5-phenyl-5,7,8,9-tetrahydro-4*H*-chromeno[2,3-*d*]pyrimidine-4,6(3*H*)-dione (6). The yield was 42%, m.p. >300 °C. Found (%): C, 71.23; H, 5.88; N, 8.41. $C_{20}H_{20}N_2O_3$. Calculated (%): C, 71.41; H, 5.99; N, 8.33. IR (ν/cm^{-1}): 3052—2656 (NH); 1672 (C=O). ^{1}H NMR, δ: 0.97, 1.08 (both s, 3 H each, C(8)$(CH_3)_2$); 2.10 (m, 2 H, CH_2); 2.24 (s, 3 H, C(2)—CH_3); 2.52 (m, 2 H, CH_2); 5.01 (s, 1 H, H(5)); 7.27 (m, 5 H, C_6H_4); 12.40 (br.s, 1 H, NH).

2-Methyl-5-(2-thienyl)-5,7,8,9-tetrahydro-4*H*-chromeno[2,3-*d*]pyrimidine-4,6(3*H*)-dione (7). The yield was 47%, m.p. 230—233 °C. Found (%): C, 61.05; H, 4.51; N, 8.82. $C_{16}H_{14}N_2O_3S$. Calculated (%): C, 61.13; H, 4.49; N, 8.91. IR (ν/cm^{-1}): 3080—2620 (NH); 1672 (C=O). ^{1}H NMR, δ: 1.99 (m, 2 H, CH_2); 2.28 (s, 3 H, CH_3); 2.38, 2.69 (both m, 2 H each, 2 CH_2); 5.04 (s, 1 H, H(5)); 6.85 (m, 2 H, H(3′), H(4′)); 7.25 (m, 1 H, H(5′)); 12.64 (br.s, 1 H, NH). ^{13}C NMR, δ: 19.78, 20.81, 26.57, 26.78, 36.24, 101.09, 114.41, 123.96, 124.21, 126.40, 147.46, 158.67, 161.91, 165.70, 195.74.

8-Acetoxy-2-methyl-5-phenyl-3,5-dihydro-4*H*-chromeno[2,3-*d*]pyrimidin-4-one (8). The yield was 75%, m.p. 295—297 °C. Found (%): C, 67.73; H, 4.74; N, 8.02. $C_{20}H_{16}N_2O_4$. Calculated (%): C, 68.96; H, 4.63; N, 8.04. IR (ν/cm^{-1}): 3050—2600 (NH); 1768 (C=O). ^{1}H NMR, δ: 2.26, 2.30 (both s, 3 H each, CH_3, C(=O)—CH_3); 5.16 (s, 1 H, H(5)); 6.89 (d, 1 H, H(7), J = 8.4 Hz); 7.03 (s, 1 H, H(9)); 7.23 (m, 6 H, C_6H_5 + H(6)); 12.45 (br.s, 1 H, NH). ^{13}C NMR, δ: 20.62, 20.82, 37.67, 99.63, 110.15, 118.35, 121.91, 126.32, 127.34, 128.28, 130.13, 145.35, 149.42, 149.63, 158.50, 161.18, 162.12, 168.72.

4-(4-Chlorophenyl)-3,7-dimethyl-1-phenyl-4,6-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidin-5(1*H*)-one (9). The yield was 68%, m.p. >300 °C. Found (%): C, 67.81; H, 4.12; N, 13.05. $C_{22}H_{17}ClN_4O_2$. Calculated (%): C, 65.27; H, 4.23; N, 13.84. IR (ν/cm^{-1}): 2950—2600 (NH). ^{1}H NMR, δ: 1.92, 2.31 (both s, 3 H each, C(6)—CH_3, C(2)—CH_3); 5.06 (s, 1 H, H(5)); 7.32—7.75 (m, 9 H, C_6H_5 + C_6H_4); 12.60 (br.s, 1 H, NH).

10-Methyl-7-phenyl-7,9-dihydro-6*H*,8*H*-benzo[*b*]pyrano[3′,4′:5,6]pyrano[2,3-*d*]pyrimidine-6,8-dione (10). The yield was 57%, m.p. >300 °C (Ref. 10: m.p. >300 °C). Found (%): C, 69.03; H, 3.99; N, 7.94. $C_{21}H_{14}N_2O_4$. Calculated (%): C, 70.39; H, 3.94; N, 7.82. IR (ν/cm^{-1}): 2950—2600 (NH); 1720 (C=O). ^{1}H NMR, δ: 2.33 (s, 3 H, CH_3); 4.86 (s, 1 H, H(7)); 7.25—7.95 (m, 9 H, (C_6H_5 + H(1)—H(4)); 12.70 (br.s, 1 H, NH). ^{13}C NMR, δ: 20.80, 34.24, 100.94, 105.02, 113.11, 116.38, 122.39, 124.61, 126.71, 127.94, 128.30, 132.63, 142.34, 151.98, 159.19, 161.70.

7-(4-Methoxyphenyl)-10-methyl-7,9-dihydro-6*H*,8*H*-benzo[*b*]thiopyrano[3′,4′:5,6]pyrano[2,3-*d*]pyrimidine-6,8-dione (11). The yield was 72%, m.p. >300 °C. Found (%): C, 66.21; H, 4.12; N, 6.84. $C_{22}H_{16}N_2O_4S$. Calculated (%): C, 65.33; H, 3.99;

N, 6.93. IR (ν/cm^{-1}): 2950—2600 (NH); 1664 (C=O). ^{1}H NMR, δ: 2.33 (s, 3 H, C(2)—CH_3); 3.67 (s, 3 H, OCH_3); 5.05 (s, 1 H, H(7)); 6.80 (d, 2 H, H(3′), H(5′), J = 8.0 Hz); 7.17 (d, 2 H, H(2′), H(6′), J = 8.2 Hz); 7.68, 8.30 (both m, 3 H, 1 H, H(1)—H(4)); 12.68 (br.s, 1 H, NH).

7-Acetoxymethyl-2-methyl-5-phenyl-3*H*,5*H*-pyrano[2′,3′:5,6]-pyrano[2,3-*d*]pyrimidine-4,9-dione (12). The yield was 52%, m.p. >300 °C. Found (%): C, 64.07; H, 4.05; N, 7.14. $C_{20}H_{16}N_2O_6$. Calculated (%): C, 63.16; H, 4.24; N, 7.36. IR (ν/cm^{-1}): 2950—2600 (NH); 1756 (C=O). ^{1}H NMR, δ: 1.99 (s, 3 H, C$\underline{H}_3$COOCH$_2$); 2.30 (s, 3 H, C(2)—CH_3); 4.88 (dd, 2 H, CH_3COOC$\underline{H}_2$, J = 14.3 Hz, J = 15.0 Hz); 5.05 (s, 1 H, H(5); 6.48 (s, 1 H, H(8)); 7.29 (m, 5 H, C_6H_5); 12.56 (br.s, 1 H, NH). ^{13}C NMR, δ: 20.25, 21.07, 38.64 (overlap with the signal for DMSO), 60.62, 98.40, 113.86, 127.58, 128.06, 128.66, 137.02, 140.23, 150.20, 159.46, 160.18, 161.82, 161.97, 169.68.

7-Acetoxymethyl-5-(4-chlorophenyl)-2-methyl-3*H*,5*H*-pyrano[2′,3′:5,6]pyrano[2,3-*d*]pyrimidine-4,9-dione (13). The yield was 69%, m.p. >300 °C. Found (%): C, 57.14; H, 3.83; N, 6.44. $C_{20}H_{15}ClN_2O_6$. Calculated (%): C, 57.91; H, 3.64; N, 6.75. IR (ν/cm^{-1}): 2950—2600 (NH); 1760 (C=O). ^{1}H NMR, δ: 2.00 (s, 3 H, C$\underline{H}_3$COOCH$_2$); 2.31 (s, 3 H, C(2)—CH_3); 4.88 (dd, 2 H, CH_3COOC$\underline{H}_2$, J = 14.6 Hz, J = 14.4 Hz); 5.09 (s, 1 H, H(5)); 6.50 (s, 1 H, H(8)); 7.31 (d, 2 H, H(2′), H(6′), J = 7.7 Hz); 7.39 (d, 2 H, H(3′), H(5′), J = 7.9 Hz); 12.63 (br.s, 1 H, NH).

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