

Full Paper

Microwave-promoted Facile and Efficient Preparation of *N*-(alkoxycarbonylmethyl) Nucleobases – Building Blocks for Peptide Nucleic Acids

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Abstract: A simple, rapid, and regioselective approach for the synthesis of *N*-(methoxycarbonylmethyl)- and *N*-(*n*-propoxycarbonylmethyl) nucleobases was developed. By using DMF as the solvent and in the presence of K₂CO₃ as the base, all the desired products were obtained in moderate yields within 8 min under microwave irradiation.

Keywords: Modified nucleoside analogues, microwave irradiation, peptide nucleic acids

Introduction

In recent years, modified nucleoside analogues have become of great interest due to their intriguing biological and pharmacological properties [1-5]. For example, a number of agents that exhibit potent anti-viral and anti-tumor activities such as AZT [6], Acyclovir [7-8], Neplanocin A [9], Peptide Nucleic Acids (PNA) [10-12] and so on have been prepared by modification of the carbohydrate ring of the natural nucleosides. PNA is a potent DNA mimic, in which the sugar-phosphate backbone of natural nucleic acids is replaced by a polyamide backbone. Since it was first reported by Nielsen and coworkers in 1991, PNA has attracted wide attention in medicinal chemistry for the development of gene therapy drugs or molecular probes. As a result, several groups have developed a variety of methods for the preparation of *N*-(alkoxycarbonylmethyl) nucleobases and their derivatives [13-17],

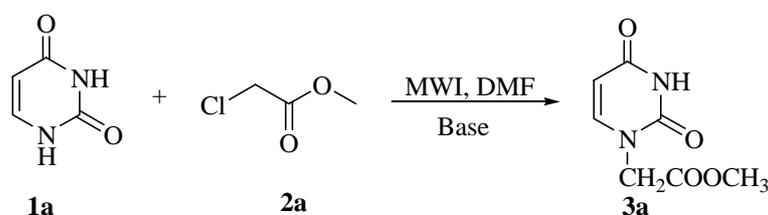
which are important building blocks for PNA. However, the reported methods have some drawbacks, such as poor yields and regioselectivity, long reaction times and harsh reaction conditions.

In order to expand our research on the modification of nucleosides [18-20] and obtain these building blocks in higher yields with shorter reaction times and under milder reaction conditions, we turned our attention to microwave irradiation (MWI). The use of microwave-assisted organic syntheses has attracted considerable interest over the last two decades, leading to remarkable decreases in reaction times, significant enhancements of yields, easier workups and better regioselectivity [21-29]. Herein, we report a rapid, facile and practical protocol for the formation of N-(methoxycarbonylmethyl)- and N-(*n*-propoxycarbonylmethyl) nucleobases.

Results and Discussion

Initially, we selected the reaction of uracil with methyl chloroacetate as a model system to investigate the influence of base and irradiation time on the yield, as summarized in Table 1.

Table 1. Optimization of Base and Irradiation Time ^a.



Entry	Base	Irradiation time/min	Yield/% ^b
1	DMAP	6	52
2	CH ₃ ONa	6	41
3	NaH	6	50
4	K ₂ CO ₃	6	64
5	K ₂ CO ₃	8	76
6	K ₂ CO ₃	9	74
7	K ₂ CO ₃	10	68

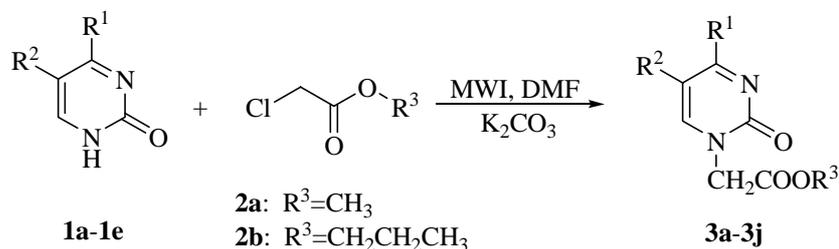
^a Reaction conditions: **1a** (2 mmol), **2a** (6 mmol), base (2 mmol), DMF (5 mL), MWI 250 W (160 °C);

^b Isolated yields based on **1a**.

All reactions were carried out in DMF, as it is an excellent solvent both for dissolving nucleobases and absorbing microwave energy. To our delight, **3a** was obtained in 52% yield by using DMAP as base (entry 1). Changing the base to CH₃ONa or NaH only led to worse results (entries 2 and 3). An obvious yield improvement was observed when K₂CO₃ was employed (entry 4). Consequently, K₂CO₃ was selected as the best base, not only because it gave rise to the best results, but also because it is very cheap and easy to handle. The irradiation time had also significant effect on the yield, but it seemed that the reaction reached chemical equilibrium after being irradiated for some 8 min, as only slight yield variations were detected after longer irradiation times (entries 5 and 6). With prolonged reaction times (entry 7) a lower yield of **3a** resulted and some N³-alkylated product was obtained. Further screening of irradiation power and reaction temperatures confirmed that 250 W and 160 °C

were the best conditions. With this promising procedure in hand, we then extended the scope of substrates to include other uracil derivatives, as outlined in Table 2.

Table 2. Alkylation of Various Uracil Derivatives in DMF under MWI ^a.



Entry	Uracil derivative	R ¹	R ²	R ³	Product	Yield/% ^b
1	1a	OH	H	CH ₃	3a	76
2	1b	OH	CH ₃	CH ₃	3b	78
3	1c	OH	Cl	CH ₃	3c	73
4	1d	OH	I	CH ₃	3d	72
5	1e	NH ₂	H	H	3e	- ^c
6	1f	NHAc	H	CH ₃	3f	64
7	1a	OH	H	CH ₂ CH ₂ CH ₃	3g	70
8	1b	OH	CH ₃	CH ₂ CH ₂ CH ₃	3h	67
9	1c	OH	Cl	CH ₂ CH ₂ CH ₃	3i	74
10	1d	OH	I	CH ₂ CH ₂ CH ₃	3j	68

^a Reaction conditions: **1** (2 mmol), **2** (6 mmol), base (2 mmol), DMF (5 mL), MWI 250 W (160 °C);

^b Isolated yields based on **1**.

^c the desired product **3e** was not obtained.

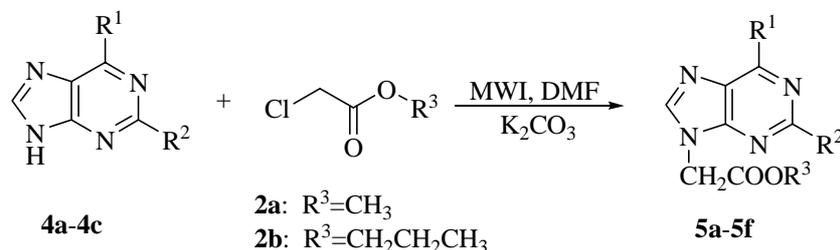
To our delight, all the uracil derivatives were exclusively alkylated at N-1, as confirmed by HMBC spectra, suggesting that our method was highly regioselective. It is worth mentioning that the same results were achieved when **2a** was employed as the alkylating agent under the same conditions (entries 6-10). Substituting 5-H with CH₃, Cl, or I only resulted in slight variations in yield, indicating that no obvious substituent-effect existed [26]. Disappointingly, alkylation of **1e** gave very poor results and only starting material was recovered. In order to increase the solubility and prevent side reactions, N⁴-acetyl cytosine (**1f**) was then utilized as the precursor of **1e** and treated with **2a** as described above to afford **3f** in 64% yield (entry 5).

Interestingly, the procedure developed for uracil derivatives also worked well for purine derivatives. As can be seen from Table 3, the length of alkyl chain in the chloroacetate reagent did not affect the yield. The target N⁹-alkylated products were produced in high regioselectivity and good yields. To our surprise, no obvious changes in yields were observed when the 6-Cl and 2-H in **4a** were substituted by 6-benzylamino (**4c**) and 2-Cl groups (**4b**), respectively. A possible explanation is that substituents in these positions do not affect the electronic nature of N-9.

In order to investigate the capability and selectivity of our method compared with the conventional heating method, the formation of **3a** was carried out in a pre-heated oil bath under the same conditions used with the microwave irradiation. It was shown the reaction afforded only 13% yield after 8 min

and 50% yield after 6 h, and that the product was associated with the N³-alkylated byproduct, clearly indicating that our method was superior to the conventional method.

Table 3. Alkylation of Various Purine Derivatives in DMF under MWI ^a.



Entry	Purine derivatives	R ¹	R ²	R ³	Product	Yield/% ^b
1	4a	Cl	H	CH ₃	5a	72
2	4b	Cl	Cl	CH ₃	5b	74
3	4c	benzylamino	H	CH ₃	5c	78
4	4a	Cl	H	CH ₂ CH ₂ CH ₃	5d	68
5	4b	Cl	Cl	CH ₂ CH ₂ CH ₃	5e	70
6	4c	benzylamino	H	CH ₂ CH ₂ CH ₃	5f	76

^a Reaction conditions: **4** (2 mmol), **2** (6 mmol), base (2 mmol), DMF (5 mL), MWI 250 W (160 °C);

^b Isolated yields based on **4**.

Conclusions

In summary, we have developed a procedure for the preparation of N-(alkoxycarbonylmethyl) nucleobases that is rapid, simple and highly efficient in terms of yield and regioselectivity. Our method has several additional advantages, such as milder reaction conditions, short reaction times and lack of side products. The use of this method to synthesize other PNA building blocks is currently under study in our laboratory and the results will be reported in due course.

Acknowledgements

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Experimental Section

General

All reagents and solvents were purchased from commercial sources and used without further purification. The nucleobases were a gift of Xinxiang Tuoxin Biochemical Technology & Science Co. Ltd, P. R. China. Melting points were determined on an XRC-1 micro melting point apparatus and are uncorrected. ¹H- and ¹³C-NMR spectra were recorded in DMSO-d₆ solutions on a Bruker DPX-400 spectrometer (at 400 MHz and 100 MHz, respectively) using TMS as internal standard. High resolution mass spectra were obtained on the electrospray ionization (ESI) mass spectrometer.

Elemental analyses were performed on an EA-1110 (CE Instruments) instrument. All reactions were performed in a commercially available single-mode microwave apparatus equipped with a high sensitivity IR sensor for temperature control and measurement (MAS-I, Sineo Microwave Chemical Technology Co. Ltd., Shanghai, China).

General Procedure for the preparation of 3a (microwave method)

A mixture of uracil (2 mmol, 0.224 g), K₂CO₃ (2 mmol, 0.276 g) and methyl chloroacetate (6 mmol, 0.55 mL) in DMF (5 mL) was placed in a 50 mL round-bottom glass flask. After being irradiated at 250 W (160 °C) for 8 min, the reaction mixture was concentrated to dryness under reduced pressure and the residue was purified by column chromatography (1:1 ethyl acetate-cyclohexane) to afford *1-(methoxycarbonylmethyl) uracil (3a)* as a white power in 76% yield; M.p. 180-182 °C (ref. 30); ¹H-NMR δ: 3.69 (s, 3H, CH₃), 4.52 (s, 2H, CH₂), 5.62 (d, 1H, *J*=8 Hz, H-5), 7.62 (d, 1H, *J*=8 Hz, H-6), 11.40 (s, 1H, H-3); ¹³C-NMR δ: 48.7 (CH₂), 52.4 (CH₃), 101.3 (C-5), 146.0 (C-6), 151.1 (C-2), 163.9 (C-4), 168.8 (C=O). The following compounds were similarly prepared:

1-(Methoxycarbonylmethyl) thymine (3b): Colorless needles; M.p. 189-190 °C (lit. [31] M.p. 189–191 °C); ¹H-NMR δ: 1.76 (d, *J*=0.4 Hz, CH₃-5), 3.69 (s, 3H, OCH₃), 4.48 (s, 2H, CH₂), 7.50 (d, 1H, *J*=0.4 Hz, H-6), 11.39 (s, 1H, H-3); ¹³C-NMR δ: 12.0 (CH₃-5), 48.5 (CH₂), 52.4 (CH₃), 108.8 (C-5), 141.7 (C-6), 151.1 (C-2), 164.5 (C-4), 168.9 (C=O).

5-Chloro-1-(methoxycarbonylmethyl) uracil (3c): Colorless needles; M.p. 203-204 °C; ¹H-NMR δ: 3.68 (s, 3H, CH₃), 4.53 (s, 2H, CH₂), 8.16 (s, 1H, H-6), 11.10 (s, 1H, H-3); ¹³C-NMR δ 48.8 (CH₂), 52.6 (CH₃), 106.5 (C-5), 143.2 (C-6), 150.2 (C-2), 159.6 (C-4), 168.5 (C=O); HR-MS calcd. for C₇H₇ClN₂O₄ 218.0094, found 218.0087; Anal. calcd. for C₇H₇ClN₂O₄ for C, 38.46, H, 3.23, N, 12.82, found C, 38.45, H, 3.18, N, 12.72.

5-Iodo-1-(methoxycarbonylmethyl) uracil (3d): Colorless plates; M.p. 197-199 °C [32]; ¹H-NMR δ: 3.69 (s, 3H, CH₃), 4.52 (s, 2H, CH₂), 8.20 (s, 1H, H-6), 11.81 (s, 1H, H-3); ¹³C-NMR δ: 48.6 (CH₂), 52.5 (CH₃), 68.4 (C-5), 150.2 (C-6), 150.8 (C-2), 161.2 (C-4), 168.6 (C=O); HR-MS calcd. for C₇H₇IN₂O₄ 309.9450, found 309.9446; Anal. calcd. for C₇H₇IN₂O₄ for C, 27.12, H, 2.28, N, 9.04, found C 27.16, H 2.23, N 9.08.

N⁴-Acetyl-1-(methoxycarbonylmethyl) cytosine (3f): Colorless needles; M.p. 186-188 °C; ¹H-NMR δ: 2.10 (s, 3H, COCH₃), 3.68 (s, 3H, OCH₃), 4.63 (s, 2H, CH₂), 7.20 (d, 1H, *J*=7.6 Hz, H-5), 8.05 (d, 1H, *J*=7.6 Hz, H-5), 10.89 (s, 1H, NH); ¹³C-NMR δ: 24.5 (COCH₃), 50.8 (OCH₃), 52.4 (NCH₂), 95.4 (C-5), 150.7 (C-6), 155.3 (C-2), 163.2 (C-4), 168.6 (COCH₃), 171.1 (C=O); HR-MS calcd. for C₉H₁₁N₃O₄ 225.0750, found 225.0746; Anal. calcd. for C₉H₁₁N₃O₄ for C, 48.00; H, 4.92; N, 18.66; O, 28.42, found C, 47.91, H, 4.87, N 18.59.

1-(n-Propoxycarbonylmethyl) uracil (3g): Colorless plates; M.p. 124-125 °C; ¹H-NMR δ: 0.88 (t, 3H, *J*=7.2 Hz, CH₃), 1.60 (m, 2H, CH₂CH₃), 4.07 (t, 2H, *J*=7.2 Hz, OCH₂), 4.52 (s, 2H, NCH₂), 5.61 (d, 1H, *J*=8 Hz, H-5), 7.62 (d, 1H, *J*=8 Hz, H-6), 11.38 (s, 1H, H-3); ¹³C-NMR δ: 10.3 (CH₃), 21.6

(CH₂CH₃), 48.8 (NCH₂), 66.7 (OCH₂), 101.2 (C-5), 146.0 (C-6), 151.1 (C-2), 163.9 (C-4), 168.3 (C=O); HR-MS calcd. for C₉H₁₂N₂O₄ 212.0797, found 212.0290; Anal. calcd. for C₉H₁₂N₂O₄ for C, 50.94; H, 5.70; N, 13.20, found C, 50.90; H, 5.61; N, 13.30.

1-(n-Propoxycarbonylmethyl) thymine (3h) Colorless plates; M.p. 140-141 °C; ¹H-NMR δ: 0.88 (t, 3H, *J*=7.2 Hz, CH₂CH₃), 1.60 (m, 2H, CH₂CH₃), 1.76 (s, 3H, CH₃-5), 4.06 (t, 2H, *J*=7.2 Hz, OCH₂), 4.47 (s, 2H, NCH₂), 7.50 (d, 1H, *J*=1.2 Hz, H-6), 11.36 (s, 1H, H-3); ¹³C-NMR δ: 10.3 (CH₂CH₃), 12.0 (CH₃-5), 21.6 (CH₂CH₃), 48.6 (NCH₂), 66.6 (OCH₂), 108.7 (C-5), 141.7 (C-6), 151.1 (C-2), 164.5 (C-4), 168.4 (C=O); HR-MS calcd. for C₁₀H₁₄N₂O₄ 226.0954, found 226.0950; Anal. calcd. for C₁₀H₁₄N₂O₄ for C, 53.09; H, 6.24; N, 12.38, found C, 53.00; H, 6.15; N, 12.30.

5-Chloro-1-(n-propoxycarbonylmethyl) uracil (3i) White power; M.p. 148-149 °C; ¹H-NMR δ: 0.88 (t, 3H, *J*=7.2 Hz, CH₂CH₃), 1.60 (m, 2H, CH₂CH₃), 4.06 (t, 2H, *J*=7.2 Hz, OCH₂), 4.52 (s, 2H, NCH₂), 8.16 (d, 1H, *J*=4 Hz, H-6), 11.97 (s, 1H, H-3); ¹³C-NMR δ: 10.3 (CH₂CH₃), 21.6 (CH₂CH₃), 48.9 (NCH₂), 66.8 (OCH₂), 106.5 (C-5), 143.3 (C-6), 150.3 (C-2), 159.6 (C-4), 168.0 (C=O); HR-MS calcd. for C₉H₁₁ClN₂O₄ 246.0407, found 246.0401; Anal. calcd. for C₉H₁₁ClN₂O₄ for C, 43.83; H, 4.50; N, 11.36, found C, 43.78; H, 4.41; N, 11.30.

5-Iodo-1-(n-propoxycarbonylmethyl) uracil (3j) Colorless needles; M.p. 156-157 °C; ¹H-NMR δ: 0.88 (t, 3H, *J*=7.2 Hz, CH₃), 1.60 (m, 2H, CH₂CH₃), 4.07 (t, 2H, *J*=7.2 Hz, OCH₂), 4.52 (s, 2H, NCH₂), 8.22 (d, 1H, *J*=4 Hz, H-6), 11.80 (s, 1H, H-3); ¹³C-NMR δ: 10.3 (CH₂CH₃), 21.7 (CH₂CH₃), 48.7 (NCH₂), 66.8 (OCH₂), 68.3 (C-5), 150.2 (C-6), 150.8 (C-2), 161.2 (C-4), 168.1 (C=O); HR-MS calcd. for C₉H₁₁IN₂O₄ 337.9763, found 337.9759; Anal. calcd. for C₉H₁₁IN₂O₄ for C, 31.97; H, 3.28; N 8.29, found C, 31.89; H, 3.20; N, 8.25.

6-Chloro-9-(methoxycarbonylmethyl) purine (5a) Colorless plates; M.p. 109-110 °C [33]; ¹H-NMR δ: 3.73 (s, 3H, CH₃), 5.29 (s, 2H, CH₂), 8.68 (s, 1H, H-8), 8.80 (s, 1H, H-2); ¹³C-NMR δ: 44.74 (CH₂), 52.8 (CH₃), 130.7 (C-5), 148.0 (C-8), 149.4 (C-4), 152.0 (C-6), 152.2 (C-2), 168.0 (C=O).

2,6-Dichloro-9-(methoxycarbonylmethyl) purine (5b) Colorless plates; M.p. 142-144 °C [34]; ¹H-NMR δ: 3.74 (s, 3H, CH₃), 5.27 (s, 2H, CH₂), 8.71 (s, 1H, H-8); ¹³C-NMR δ: 44.48 (CH₂), 52.9 (CH₃), 130.3 (C-5), 149.0 (C-8), 150.1 (C-4), 151.5 (C-6), 153.7 (C-2), 167.8 (C=O).

6-Benzylamino-9-(methoxycarbonylmethyl) purine (5c) Pale yellow power; M.p. 138-139 °C; ¹H-NMR δ: 3.70 (s, 3H, CH₃), 4.72 (s, 2H, CH₂Ph), 5.10 (s, 2H, NCH₂), 7.19~7.36 (m, 5H, Ph), 8.14 (s, 1H, H-8), 8.19 (s, 1H, H-2), 8.39 (s, 1H, NH); ¹³C-NMR δ: 43.1 (CH₂Ph), 44.0 (NCH₂), 52.6 (CH₃), 119.5 (C-5), 126.8, 127.7, 128.4 (Ph), 140.3 (C-8), 141.4 (C-4), 152.8 (C-2), 154.6 (C-6), 168.6 (C=O); HR-MS calcd. for C₁₅H₁₅N₅O₂ 297.1226, found 297.1220; Anal. calcd. for C₁₅H₁₅N₅O₂ for C, 60.60; H, 5.09; N, 23.56, found C, 60.53; H, 5.02; N, 23.60.

6-Chloro-9-(n-propoxycarbonylmethyl) purine (5d) Yellow power; M.p. 56-58 °C; ¹H-NMR δ: 0.84 (t, 3H, *J*=7.2 Hz, CH₃), 1.59 (m, 2H, CH₂CH₃), 4.09 (t, 2H, *J*=7.2 Hz, OCH₂), 5.29 (s, 2H, NCH₂), 8.69 (s, 1H, H-8), 8.19 (s, 1H, H-2); ¹³C-NMR δ: 10.2 (CH₂CH₃), 21.5 (CH₂CH₃), 44.8 (NCH₂), 67.1

(OCH₂), 130.7 (C-5), 148.0 (C-8), 149.4 (C-4), 152.0 (C-6), 152.2 (C-2), 167.5 (C=O); HR-MS calcd. for C₁₀H₁₁ClN₄O₂ 254.0571, found 254.0562; Anal. calcd. for C₁₀H₁₁ClN₄O₂ for C, 47.16; H, 4.35; N, 22.00, found C, 47.09; H, 4.27; N, 21.89.

2,6-Dichloro-9-(n-propoxycarbonylmethyl) purine (5e) Colorless rod-like crystals; M.p. 117-119 °C; ¹H-NMR δ: 0.86 (t, 3H, *J*=7.2 Hz, CH₂CH₃), 1.60 (m, 2H, CH₂CH₃), 4.11 (t, 2H, *J*=7.2 Hz, OCH₂), 5.27 (s, 2H, NCH₂), 8.71 (s, 1H, H-8); ¹³C-NMR δ: 10.2 (CH₃), 21.6 (CH₂CH₃), 45.0 (NCH₂), 67.2 (OCH₂), 130.3 (C-5), 149.0 (C-8), 150.1 (C-4), 151.5 (C-6), 153.8 (C-2), 167.3 (C=O); HR-MS calcd. for C₁₀H₁₀Cl₂N₄O₂ 288.0181, found 288.0178; Anal. calcd. for C₁₀H₁₀Cl₂N₄O₂ for C, 41.54; H, 3.49; N, 19.38, found C, 41.45; H, 3.41; N, 19.46.

6-Benzylamino-9-(n-propoxycarbonylmethyl) purine (5f) Colorless plates; M.p. 179-180 °C; ¹H-NMR δ: 0.85 (t, 3H, *J*=7.2 Hz, CH₃), 1.59 (m, 2H, CH₂CH₃), 4.07 (t, 2H, *J*=7.2 Hz, OCH₂), 4.72 (s, 2H, CH₂Ph), 5.09 (s, 2H, NCH₂), 7.19~7.36 (m, 5H, Ph), 8.14 (s, 1H, H-8), 8.19 (s, 1H, H-2), 8.34 (s, 1H, NH); ¹³C-NMR δ: 10.2 (CH₃), 21.6 (CH₂CH₃), 43.1 (CH₂Ph), 44.1 (NCH₂), 66.8 (OCH₂), 118.8 (C-5), 126.8, 127.3, 128.3 (Ph), 140.3 (C-8), 141.4 (C-4), 152.8 (C-6), 154.8 (C-2), 168.1 (C=O); HR-MS calcd. for C₁₇H₁₉N₅O₂ 325.1539, found 325.1536; Anal. calcd. for C₁₇H₁₉N₅O₂ for C, 62.75; H, 5.89; N, 21.52, found C, 62.68; H, 5.80; N, 21.60.

Synthesis of **3a** (conventional method)

A mixture of uracil (2 mmol, 0.224 g), K₂CO₃ (2 mmol, 0.276 g) and methyl chloroacetate (6 mmol, 0.55 mL) in DMF (5 mL), contained in a 50 mL round-bottom glass flask, was stirred under reflux in an oil-bath (160 °C) for 8 min or 6 h. The workups were performed as described above for the microwave method.

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Sample Availability: Samples of the compounds mentioned are available from authors.