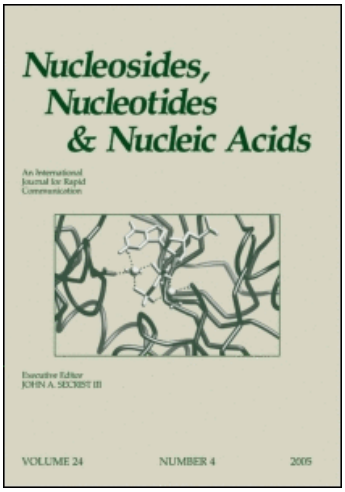

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SYNTHESIS OF *N*-ARYL URACILS AND HYPOXANTHINES AND THEIR BIOLOGICAL PROPERTIES

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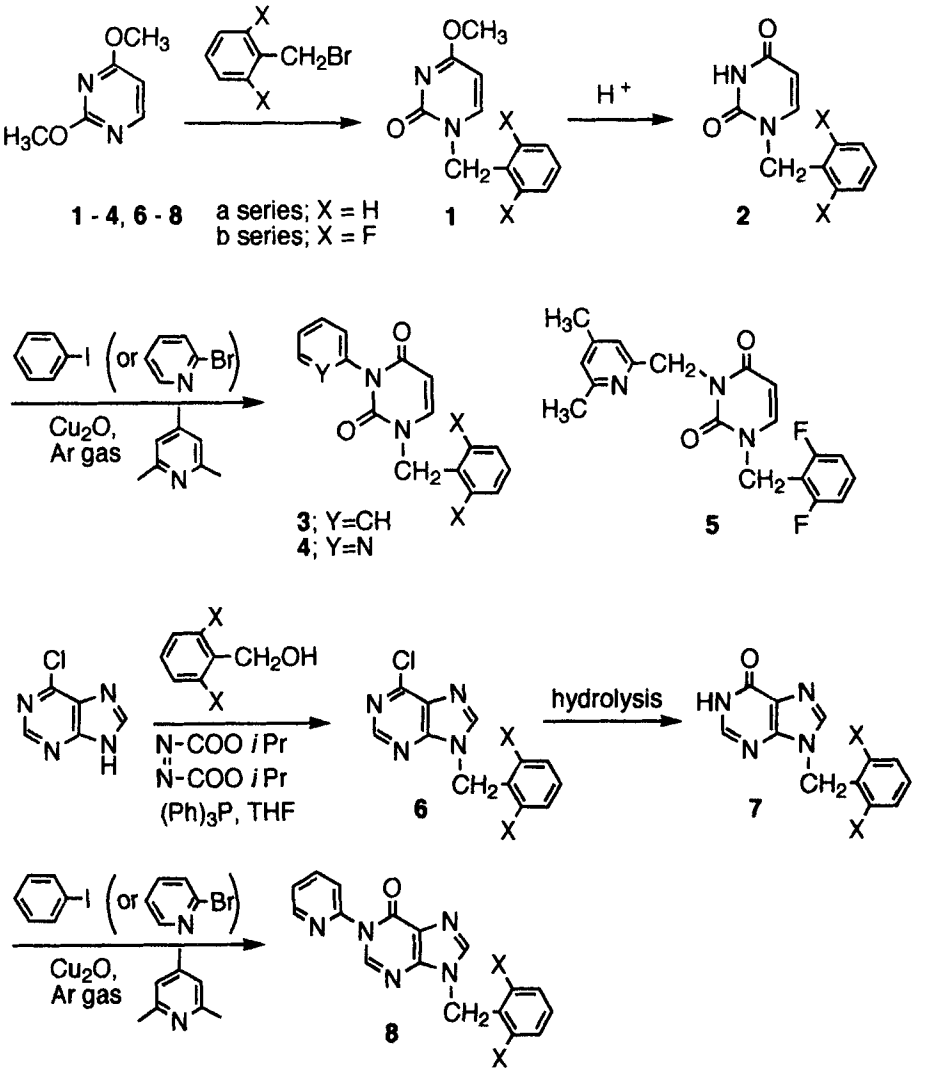
ABSTRACT: 1-Benzyluracils **2a,b** were treated with iodobenzene in the presence of cuprous oxide in 2,4,6-trimethylpyridine at 180℃ to give the N^1-phenyl derivatives **3a** and **3b** in 47% and 55%, respectively. Similar reaction of **2a** with 2-bromopyridine at 120℃ gave the 3-(2-pyridinyl)uracil **4a** in 42% yield. However, unusual product **5** as well as 3-(2-pyridinyl) derivative **4b** were obtained in the case of **2b**. The structure of **5** was identified as 1-(2,6-difluorobenzyl)-3-[(2,4-dimethyl-2-pyridinyl)methyl]uracil from spectroscopic data. Reaction of the hypoxanthines **7a,b** with 2-bromopyridine gave the 1-(2-pyridinyl)hypoxanthines **8a,b** in low yields. But *N*-phenylation of **7a,b** were unsuccessful.

INTRODUCTION

Since treatment of epilepsy by drugs fail to control seizure satisfactory and experience significant side effects in many case, the need for improved drug is increasing.[1,2] Kelley *et al.* reported the syntheses and anticonvulsant activities of 9-(2-fluorobenzyl)-6-methyladenine (BW A78U)[3] and its carbon-nitrogen isostere (534U87).[4] Recently, uridine was identified as a sleep-promoting substances[5] and N^3-benzyluridine was found to have CNS-depressant effects.[6] These backgrounds prompted us to investigate the synthesis of the *N*-aryl derivatives of 1-benzyluracils and hypoxanthines.



SCHEME

RESULTS AND DISCUSSION

We reported a new method for the synthesis of N^3-phenyluridne using a method similar to the Gabriel synthesis[7,8] and this method was applied to 1-benzyluracils.

1-Benzyluracils **2a,b** were prepared from 2,4-dimethoxypyrimidine via 4-methoxy-2(1*H*)-pyrimidinones **1a,b** in a similar manner for the synthesis of 1-methyluracil.[9] Thus reaction of **2a** with iodobenzene in the presence of cuprous oxide in 2,4,6-trimethylpyridine

at 180 ℃ gave **3a** in 47%. Compound **3a** showed similar UV spectrum to that of 3-phenyluridine, suggesting N^3-phenyluracil structure. Analytical data also supported the structure of **3a**. This reaction was applied to the 2,6-difluorobenzyluracil **2b**. 3-Phenyl derivative **3b** was obtained in 55% yield and recovered starting material in 9.1%. Compound **2a** was also treated with 2-bromopyridine at 120℃ using the same catalyst and solvent to give the 3-(2-pyridinyl)uracil **4a** in 42% yield. Similar reaction of **2b** with 2-bromopyridine was carried out to afford the desired product **4b** and unusual product **5** in 52% and 14.6%, respectively. The UV spectrum suggested that compound **5** is N^3-alkylated product. The ^{1}H-NMR spectrum revealed appearance of two singlet at 2.20 and 2.42 ppm attributable to methyl protons. Signals of two methylene protons were also observed at 5.05 and 5.20 ppm, indicating 1-(2,6-difluorobenzyl)-3-[(2,4-dimethyl-6-pyridinyl)methyl] uracil structure. Mass spectroscopic data (M^+, m/z 251) also supported the structure. The reaction mechanism to form **5** is under investigation.

9-Benzylhypoxanthine **7a** was prepared by hydrolysis of 9-benzyl-6-chloropurine **6a**.[10,11] 9-(2,6-Difluorobenzyl)hypoxanthine **7b** was also prepared by hydrolysis of 6-chloro-9-(2,6-difluorobenzyl)purine **6b**. The hypoxanthines **7a,b** were treated with with 2-bromopyridine in a manner similar to that of **4a** to give the 2-pyridinyl derivatives **8a** and **8b** in low yields. But *N*-phenylation of **7a,b** was unsuccessful. In the case of **7b** unknown product was obtained.

Preliminary biological activities of compounds **2b**, **4b**, **6b** and **7b** were evaluated. No significant response was observed in the assay of convulsion by maximal electroshock.[3,4] However, compound **6b** showed weak inhibition activity against phosphodiesterase I (IC_{50} 18 μg/ml).

EXPERIMENTAL

Melting points (mp) were determined using a Yanagimoto micro-melting point

apparatus (hot stage type) and are uncorrected. UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. Low resolution mass spectra were obtained on a Shimadzu-LKB 9000B mass spectrometer in the direct-inlet mode. High resolution mass spectra were obtained on a JMS AX-500 spectrometer in the direct-inlet mode. ^{1}H-NMR spectra were recorded on either Varian UNITY 200 (200 MHz) or Varian UNITY 600 (600 MHz) in $CDCl_3$ (or dimethyl sulfoxide (DMSO)-d_6) with tetramethylsilane as an internal standard. Merck Art 5554 plates precoated with silica gel 60 containing fluorescent indicator F_{254} were used for thin-layer chromatography and silica gel 60 (Merck 7734, 60 - 200 mesh) was employed for column chromatography.

1-Benzyl-4-methoxy-2(1*H*)-pyrimidinone (1a). A mixture of 2,4-dimethoxypyrimidine (4.22 g, 30.1 mmol) and benzyl bromide (36 ml, 10 eq.) was kept at 40 ℃ overnight. The crystals were collected by filtration and the filtrate was applied to the column of silica gel G (3.3 × 30 cm). The column was washed with benzene (1 l) and eluted with $CHCl_3$ (1 l) and the fraction of the product was concentrated to afford another crystals. Yield 4.56 g (70%). mp 113-117℃. UV λ max (MeOH) 277 nm. MS *m/z*: 216 (M^+), 201 (M^+-CH_3). ^{1}H-NMR (DMSO-d_6) δ : 7.2-7.5 (6H, m, H6, C_6H_5), 5.85 (1H, d, J = 7.3 Hz, H5), 5.06 (2H, s, -CH_2-), 3.97 (3H, s, OCH_3).

1-Benzyluracil (2a). To a suspension of **1a** (2.17 g, 10 mmol) in 1,4-dioxane (50 ml) was added concentrated HCl and the solution was heated under reflux for 1 h, then cooled. Recrystallization of the product from EtOH gave white crystals (1.33 g, 66%). mp 169-171℃ (lit.[12] 175℃). *Anal.* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.08; H, 4.98; N, 13.61. MS *m/z*: 202 (M^+). UV λ max (MeOH) 265 nm. ^{1}H-NMR (DMSO-d_6) δ : 11.33 (1H, br s, N^3-H), 7.76 (1H, d, J = 7.88 Hz, H6), 7.25 - 7.42 (5H, m, Ph), 5.60 (1H, d, J = 7.69 Hz, H5), 4.88 (2H, s, -CH_2-).

1-(2,6-Difluorobenzyl)-4-methoxy-2(1*H*)-pyrimidinone (1b). To a solution of 2,4-dimthoxypyrimidine (1.32 g, 10 mmol) in dry THF (10 ml) was added 2,6-difluorobenzyl bromide (2.07 g, 10 mmol) and the solution was heated at 80℃ for 1 h. After cooling, the solution was diluted with AcOEt (10 ml) and chromatographed over a column of silica gel G (3.0×45 cm) using a gradient of hexane-AcOEt = 1:1 and AcOEt as a eluant. Evaporation of the fraction and crystallization from AcOEt gave white crystals (1.08 g, 42%). mp 143-145℃. *Anal.* Calcd for $C_{12}H_{10}F_2N_2O_2$: C, 57.15; H, 4.00; N, 11.11. Found: C, 57.15; H, 3.98; N, 11.01. MS *m/z*: 252 (M^+). UV λ max (MeOH) 274 nm. ^{1}H-NMR ($CDCl_3$) δ : 7.4 0 (1H, dt, J = 7.33, 1.10 Hz, H6), 7.30 (1H, m, H4'), 6.94 (2H, m, H3', H5'), 5.84 (1H, d, J = 7.33 Hz, H5), 5.12 (2H, s, -CH_2-), 3.94 (3H, s, OCH_3).

1-(2,6-Difluorobenzyl)uracil (2b). A solution of **1b** (252 mg, 1 mmol) in a mixture of 1,4-dioxane (50 ml) and concentrated HCl (0.1 ml) was heated under reflux for 1 h, then cooled. Concentration of the solution afforded solid, which was recrystallized from EtOH to give white crystals (190 mg, 79%). mp 226-227℃. *Anal.* Calcd for $C_{11}H_8F_2N_2O_2$: C, 55.47; H, 3.39; N, 11.76. Found: C, 55.43; H, 3.32; N, 11.59. MS *m/z*: 238 (M^+). UV λ max (MeOH) 263 nm. ^{1}H-NMR (DMSO-d_6) δ : 11.27 (1H, br s, N^3-H), 7.71 (1H, dt, J = 7.88, 1.28 Hz, H6), 7.43 (1H, m, H4'), 7.12 (2H, m, H3', H5'), 5.58 (1H, d, J = 8.06 Hz, H5), 4.95 (2H, s, -CH_2-).

1-Benzyl-3-phenyluracil (3a). To a solution of **2a** (404 mg, 2 mmol) and cupper(I) oxide (286 mg, 2 mmol) in 2,4,6-trimethylpyridine (5 ml) was added iodobenzene (1.2 ml, 10.7 mmol) and the solution was heated at 180℃ under Ar atmosphere for 20 h. Reaction was continued with additional iodobenzene (1.2 ml, 10.7

mmol) for further 20 h and the solution was diluted with CH_2Cl_2 (80 ml). The insoluble was removed by filtration and the filtrate was applied to a column of silica gel G, then eluted with 17% AcOEt in hexane and hexane-AcOEt = 1 : 2. The second fraction was evaporated and the residue was crystallized from AcOEt to give white crystals (259.6 mg, 47%). mp 161-162 °C. *Anal.* Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.26; H, 4.98; N, 10.01. MS *m/z*: 278 (M^+). UV λ max (MeOH) 266 nm. ^{1}H-NMR ($CDCl_3$) δ : 7.21 - 7.55 (11H, m, Ph, N^3-Ph, H6), 5.85 (1H, d, J = 8.06 Hz, H5), 4.95 (2H, s, $-CH_2-$).

1-Benzyl-3-(pyridin-2-yl)uracil (4a). To a solution of **2a** (202 mg, 1 mmol) and cupper(I) oxide (143 mg, 1 mmol) in 2,4,6-trimethylpyridine (6 ml) was added 2-bromopyridine (0.48 ml, 5 mmol) and the solution was heated at 120 °C under Ar atmosphere for 20 h. Work-up of the solution in a manner similar to that described in the section of **3a** gave a caramel (114 mg, 42%). mp 133-134 °C. *Anal.* Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.90; H, 4.64; N, 14.86. High-resolution MS *m/z* Calcd for $C_{16}H_{13}N_3O_2$ (M^+) 279.1008. Found: 279.0991. UV λ max (MeOH) 264 nm. ^{1}H-NMR ($CDCl_3$) δ : 8.71 (1H, m, Py 1H), 7.89 (1H, dt, J = 1.65, 7.51Hz, Py 1H), 7.23 - 7.44 (8H, m, Ph, Py 2H, H6), 5.85 (1H, d, J = 7.69 Hz, H5), 4.95 (2H, s, $-CH_2-$).

1-(2,6-Difluorobenzyl)-3-phenyluracil (3b). A solution of **2b** (238 mg, 1 mmol) and cupper(I) oxide (143 mg, 1 mmol) in the mixture of 2,4,6-trimethylpyridine (5 ml) and iodobenzene (0.6 ml, 5.4 mmol) was heated at 180 °C under Ar atmosphere for 20 h. The resulting solution was worked up in a manner similar to that described in the section of **3a** to give white crystals (176 mg, 55%). mp 183-184 °C . *Anal.* Calcd for

$C_{17}H_{12}F_2N_2O_2$: C, 64.97; H, 3.85; N, 8.91. Found: C, 64.78; H, 3.85; N, 8.83. MS *m/z*: 314 (M^+). UV λ max (MeOH) 264 nm. ^{1}H-NMR ($CDCl_3$) δ : 7.31-7.52 (7H, m, Ph, H4', H6), 6.92-7.28 (2H, m, H3', H5'), 5.86 (1H, d, J = 8.06 Hz, H5), 5.04 (2H, s, -CH_2-). Evaporation of second fraction gave starting material **2b** (22.1 mg, 9.1%).

Reaction of 1-(2,6-difluorobenzyl)uracil 2b with 2-bromopyridine. A solution of **2b** (238 mg, 1 mmol) and cupper(I) oxide (143 mg, 1 mmol) in the mixture of 2,4,6-trimethylpyridine (5 ml) and 2-bromopyridine (0.48 ml, 5 mmol) was heated at 130 ℃ under Ar atmosphere for 20 h. The resulting solution was worked up in a manner similar to that described in the section of **3a** to afford three compounds. First fraction: starting material (white crystals, 11 mg, 4.5%). Second fraction: 1-(2,6-difluorobenzyl)-3-[(2,4-dimethyl-2-pyridinyl)methyl]uracil **5** (a caramel, 46.9 mg, 15%), MS *m/z*: 357 (M^+), High-resolution MS *m/z* Calcd for $C_{19}H_{17}F_2N_3O_2$ (M^+) 357.1290. Found: 357.1269. UV λ max (MeOH) 263 nm. ^{1}H-NMR ($CDCl_3$) δ : 7.30 (2H, m, H6, H4'), 6.92-7.00 (2H, m, H3', H5'), 6.80 (1H, s, Py H5), 6.64 (1H, s, Py H3), 5.80 (1H, d, J = 8.06 Hz, H5), 5.20 (2H, s, N^3-CH_2), 5.05 (2H, s, N^1-CH_2), 2.42 (3H, s, CH_3), 2.20 (3H, s, CH_3). Third fraction: 1-(2,6-difluorobenzyl)-3-(2-pyridinyl)uracil **4b** (a caramel, 168 mg, 52%), MS *m/z*: 315(M^+), High-resolution MS *m/z* Calcd for $C_{16}H_{11}F_2N_3O_2$ (M^+) 315.0820. Found: 315.0800. UV λ max (MeOH) 263 nm. ^{1}H-NMR ($CDCl_3$) δ : 8.65(1H, br s, Py 1H), 7.82-7.91 (1H, dt, J = 2.01, 7.69Hz, Py 1H), 7.27-7.42 (4H, m, Py 2H, H6, H4'), 6.91-6.99 (2H, m, H3', H5'), 5.86 (1H, d, J = 8.06 Hz, H5), 5.02 (2H, s, -CH_2-).

9-Benzylhypoxanthine (7a). A solution of 6-chloro-9-benzylpurine **6a**[10,11] (245 mg, 1 mmol) in 1M HCl (5 ml) was heated under reflux for 1 h and the solution was concentrated to give white crystals, which was recrystallized from EtOH (192 mg, 84%).

mp 284.5-286.5℃. *Anal.* Calcd for $C_{12}H_{10}N_4O$: C, 63.66; H, 4.46; N, 24.76. Found: C, 63.56; H, 4.47; N, 24.65. MS *m/z*: 226 (M^+). UV λ max (MeOH) 250 nm. ^{1}H-NMR (DMSO-d_6) δ : 12.31 (1H, br s, N^1-H), 8.22 (1H, s, H8), 8.06 (1H, d, *J* =2.47, H2), 7.28-7.35 (5H, m, Ph), 5.38 (2H, s, -CH_2-).

Phenylation of 9-benzylhypoxanthine (7a). A solution of **7a** (226 mg, 1 mmol) and cupper(I) oxide (143 mg, 1 mmol) in the mixture of 2,4,6-trimethylpyridine (5 ml) and iodobenzene (0.6 ml, 5.4 mmol) was heated at 130℃ under Ar atmosphere for 20 h. Spots of **7a** and desired product were not observed on TLC.

9-Benzyl-1-(pyridin-2-yl)hypoxanthine (8a). To a solution of **7a** (226 mg, 1 mmol) and cupper(I) oxide (143 mg, 1 mmol) in 2,4,6-trimethylpyridine (6 ml) was added 2-bromopyridine (0.48 ml, 5 mmol) and the solution was heated at 100℃ under Ar atmosphere for 20 h. Reaction was continued for further 44 h at 120℃ and work-up of the solution in a manner similar to that described in the section of **3a** gave a solid, which was crystallized from benzene to give white crystals (45 mg, 15%). mp 153℃. *Anal.* Calcd for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.21; H, 4.35 ; N, 23.04. MS *m/z*: 303 (M^+). UV λ max (MeOH) 256 nm. ^{1}H-NMR ($CDCl_3$) δ : 8.59-8.63 (1H, m, Py H2), 8.53 (1H, s, H2), 7.88-7.91 (2H, m, Py H4, Py H5), 7.79 (1H, s, H8), 7.27-7.43 (6H, m, Ph, Py H3), 5.38 (2H, s, -CH_2-).

6-Chloro-9-(2,6-difluorobenzyl)purine (6b). To a solution of 6-chloropurine (154 mg, 1 mmol) was suspended in DMF (10 ml) was added dry K_2CO_3 (138 mg, 1 mmol) and the solution was stirred at 100℃ for 30 min. 2,6-Difluorobenzyl bromide (207 mg, 1 mmol) was added to the solution and stirring was continued at 50℃ for further 1 h.

After cooling, the insolubles were removed by filtration and the filtrate was evaporated. The residue was chromatographed over a column of silica gel G (ϕ 3×40 cm) using a gradient hexane-AcOEt = 1 : 2 and AcOEt to give white crystals (120 mg, 42%). mp147-148℃. *Anal.* Calcd for $C_{12}H_7ClF_2N_4$: C, 51.35; H, 2.51; N, 19.96. Found: C, 51.40; H, 2.58; N, 20.02. MS *m/z*: 280, 282 (M^+). UV λ max (MeOH) 264 nm. ^{1}H-NMR ($CDCl_3$) δ : 8.80 (1H, s, H2), 8.18 (1H, s, H8), 7.38 (1H, m, H4'), 6.99 (2H, m, H3', H5'), 5.56 (2H, s, $-CH_2-$).

9-(2,6-Difluorobenzyl)hypoxanthine (7b). A mixture solution of **6b** (840 mg, 3 mmol) and NaOAc (738 mg, 9 mmol) in AcOH (15 ml) was stirred at 120℃ for 5 h, then cooled. The solution was evaporated to give a residue, to which water (20 ml) was added to give white crystals (694 mg, 88%). mp 302-303℃. *Anal.* Calcd for $C_{12}H_8F_2N_4O$: C, 54.97; H, 3.07; N, 21.37. Found: C, 54.80 ; H, 3.13; N, 21.24. MS *m/z*: 262 (M^+). UV λ max (MeOH) 250 nm. ^{1}H-NMR (DMSO-d_6) δ : 12.29 (1H, br s, N^1-H), 8.10 (1H, s, H8), 8.03 (1H, s, H2), 7.49 (1H, m, H4'), 7.26 (2H, m, H3', H5'), 5.46 (2H, s, $-CH_2-$).

Reaction of 9-(2,6-difluorobenzyl)hypoxanthine 7b with iodobenzene. A solution of **7b** (262 mg, 1 mmol) and cupper(I) oxide (143 mg, 1 mmol) in the mixture of 2,4,6-trimethylpyridine (5 ml) and iodobenzene (0.6 ml, 5.36 mmol) was heated at 130℃ under Ar atmosphere for 40 h. The resulting solution was worked up in a manner similar to that described in the section of **3a** to give unknown product as a caramel (67.1 mg), structure of which could not determine by spectroscopic methods.

9-(2,6-Difluorobenzyl)-1-(2-pyridinyl)hypoxanthine (8b). A solution of **7b** (393 mg, 1.5 mmol) and cupper(I) oxide (143 mg, 1 mmol) in the mixture of 2,4,6-

trimethylpyridine (5 ml) and 2-bromopyridine (0.72 ml, 7.5 mmol) was heated at 120°C under Ar atmosphere for 20 h. The resulting solution was worked up in a manner similar to that described in the section of **3a** to give pale brownish crystals (103 mg, 20%). mp 169-171°C. *Anal.* Calcd for $C_{17}H_{11}F_2N_5O$: C, 60.18; H, 3.27; N, 20.52. Found: C, 60.10; H, 3.35; N, 20.56. MS *m/z*: 339 (M^+). UV λ max (MeOH) 256 nm. ^{1}H-NMR ($CDCl_3$) δ: 8.59-8.61 (1H, m, Py H2), 8.55 (1H, s, each H2 or H8), 7.85-7.91 (3H, m, Py H4, Py H5, each H2 or H8), 7.35-7.40 (2H, m, Py H3, H4'), 6.96-7.00 (2H, m, H3', H5'), 5.47 (2H, s, $-CH_2-$).

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