Synthesis of Tetracyclic Pyrido[2,3-*b*]azepine Derivatives as Analogues of Mirtazapine *via N*-Acyliminium Ion Cyclization

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Tetracyclic pyrido[2,3-*b*]azepine derivatives **4a-d** and **4f** as analogues of mirtazapine were synthesized *via N*-acyliminium ion cyclization by using aromatic rings such as benzene and thiophene ring as a π-nucleophile, and evaluated for the binding affinity for α_2-adrenoceptor. Among tested compounds, 2,3,9,13b-tetrahydro-1*H*-benzo[*f*]pyrrolo[2,1-*a*]pyrido[2,3-*c*]azepine (**4a**) was the most potent (*K*i = 0.26 μM) but showed about 3-fold less binding affinity than mirtazapine (*K*i = 0.08 μM) for α_2-adrenoceptor.

Key Words : Pyrido[2,3-*b*]azepine, *N*-Acyliminium ion cyclization, α_2-Adrenoceptor, Mirtazapine

Introduction

Tetracyclic azepines are presented as an important class of heterocyclic skeletons occurring in a number of bioactive molecules for a variety of biological targets[1] and form, in particular, the tetracyclic antidepressants such as mianserin (**1**, Bolvidon®) and mirtazapine (**2**, Remeron®): Mirtazapine enhances noradrenaline (NA) and serotonin (5-HT) release by blocking the inhibitory presynaptic α_2-adrenergic auto-receptors and stimulating the 5-HT_{1A} receptors.[2,3] Therefore, many synthetic efforts have been directed toward synthesis of tetracyclic azepine derivatives because of their unique structural features and biological activities.[4] Recently, we have also reported the synthesis of dibenzo[*c,f*]azepine and benzo[*f*]thieno[3,2-*c*]azepine derivatives (**3**) as analogues of mianserin.[5]

In this work, we wish to describe the synthesis and the binding affinities of tetracyclic pyrido[2,3-*b*]azepine derivatives **4** for α_2-adrenoceptor as analogues of mirtazapine including the binding affinities data of benzo[*b*]azepine derivatives **3**.

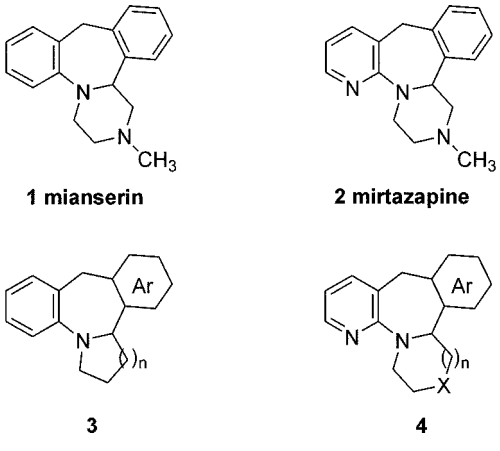


Figure 1. Representative tetracyclic azepine compounds.

Experimental Section

Materials and measurements. All compounds used in the synthesis were of reagent grade and used without further purification, and the solvents were freshly distilled by using standard purification methods. ^{1}H NMR spectra were recorded on a Gemini Varian-300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Gemini Varian-300 (75 MHz) spectrometer. Infrared (IR) spectra were recorded on Perkin Elmer 16-PC FT-IR using a potassium bromide pellet. Low (EI) resolution mass spectra were determined on HP GC 5972 and HP MS 5988A system at 70 eV. Dibenzo-[*c,f*]azepines (**3a-b**) and benzo[*f*]thieno[3,2-*c*]azepines (**3c-d**) were obtained by the procedure reported in the literature.[5]

General procedure for the preparation of cyclic imides (6a-f). To a solution of 3-benzyl-2-aminopyridine (**5a**, 2.9 g, 15.2 mmol) in 50 mL of xylene was added succinic anhydride (2.3 g, 22.9 mmol). The reaction mixture was heated at reflux for 5 h with Dean-Stark. After cooling to room temperature, the Dean-Stark was removed and acetyl chloride (2.7 mL, 30.5 mmol) was added to the mixture. The reaction mixture was heated again at reflux for 3 h. The solvent was distilled off under reduced pressure and the residue was dissolved in 100 mL of EtOAc. The organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, concentrated, and purified by flash column chromatography (EtOAc/*n*-hexane = 1 : 3) to afford **6a** (3.1 g, 75%) as a white solid: mp 128-130 °C; MS *m/z*: 266 (M^+); IR (KBr) 3018, 1790, 1712, 1578 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 4.7, 1.6 Hz, 1H, pyridine C2-H), 7.63 (dd, *J* = 7.7, 1.2 Hz, 1H, pyridine C4-H), 7.35-7.19 (m, 4H, pyridine C3-H, phenyl), 7.06 (d, *J* = 6.5 Hz, 2H, phenyl), 3.92 (s, 2H, pyridine-C$\underline{H}_2$-Ar), 2.72 (m, 2H, 2 ×-N-CO-C$\underline{H}_a$-), 2.52 (m, 2H, 2 ×-N-CO-C$\underline{H}_b$-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 148.4, 145.7, 140.5, 138.3, 135.1, 129.1, 127.3, 127.2, 125.1, 37.8, 28.9.

Preparation of 6b. The reaction of **5a** (400 mg, 2.2 mmol) and glutaric anhydride (374 mg, 3.3 mmol) afforded **6b** (233 mg, 38%) as a white solid according to the pro-

cedure described above: mp 102-103 °C; MS *m/z*: 280 (M^+); IR (KBr) 3395, 2917, 1735, 1686, 1434 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.0 Hz, 1H, pyridine C2-H), 7.53 (d, *J* = 7.6 Hz, 1H, pyridine C4-H), 7.32-7.23 (m, 5H, phenyl), 7.11 (d, *J* = 7.5 Hz, 1H, pyridine C3-H), 3.82 (s, 2H, pyridine-C$\underline{H}_2$-Ar), 2.81-2.55 (m, 4H, 2 ×O=C-C$\underline{H}_2$-), 2.12-1.94 (m, 2H, O=C-CH$_2$-C$\underline{H}_2$-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 153.9, 152.7, 144.7, 144.3, 140.4, 134.7, 134.4, 133.9, 131.9, 129.8, 41.3, 37.5, 22.4.

Preparation of 6c. Prepared from **5a** (1.64 g, 8.9 mmol) and diglycolic anhydride (1.56 g, 13.4 mmol) as described above. A yellow oil (1.05 g, 41%): MS *m/z*: 282 (M^+); IR (KBr) 3425, 2924, 1696, 1581 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.6 Hz, 1H, pyridine C2-H), 7.62 (d, *J* = 7.7 Hz, 1H, pyridine C4-H), 7.37-7.13 (m, 5H, phenyl), 7.12 (d, *J* = 7.0 Hz, 1H, pyridine C3-H), 4.41 and 4.31 (ABq, *J* = 16.5 Hz, 2H, pyridine-C$\underline{H}_2$-Ar), 3.87 (s, 4H, 2 ×O=C-C$\underline{H}_2$-O-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 156.4, 148.1, 140.1, 139.1, 129.6, 129.1, 128.9, 127.1, 125.5, 67.5, 36.3.

Preparation of 6d. Prepared from **5a** (600 mg, 3.3 mmol) and thiodiglycolic anhydride (737 mg, 4.9 mmol)) as described above. A brown solid (461 mg, 47%): mp 83-87 °C; MS *m/z*: 298 (M^+); IR (KBr) 3395, 2924, 2388, 1730, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.7, 1.7 Hz, 1H, pyridine C2-H), 7.53 (dd, *J* = 7.7, 1.7 Hz, 1H, pyridine C4-H), 7.32-7.23 (m, 5H, phenyl), 7.13 (d, *J* = 7.3 Hz, 1H, pyridine C3-H), 3.83 (s, 4H, 2 ×O=C-C$\underline{H}_2$-S-), 3.67 and 3.48 (ABq, *J* = 16.7 Hz, 2H, pyridine-C$\underline{H}_2$-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 148.3, 148.2, 140.0, 138.2, 135.4, 129.7, 129.0, 127.2, 125.0, 37.1, 32.7.

Preparation of 6f. Prepared from **5b** (2.76 g, 14.5 mmol) and glutaric anhydride (2.48 g, 21.8 mmol) as described above. A yellow oil (2.90 g, 70%): MS *m/z*: 286 (M^+); IR (KBr) 3405, 2926, 1734, 1686, 1581 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 4.8, 1.7 Hz, 1H, pyridine C3-H), 7.71 (d, *J* = 6.5 Hz, 1H, pyridine C4-H), 7.39 (dd, *J* = 7.7, 4.9 Hz, 1H, pyridine C3-H), 7.18 (d, *J* = 4.1 Hz, 1H, thienyl C3-H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H, thienyl C4-H), 6.76 (d, *J* = 3.3 Hz, 1H, thienyl C5-H), 4.01 (s, 2H, pyridine-C$\underline{H}_2$-Ar), 2.83-2.70 (m, 4H, 2 ×O=C-C$\underline{H}_2$-), 2.15-1.95 (m, 2H, O=C-CH$_2$-C$\underline{H}_2$-CH$_2$-).

General procedure for the preparation of hydroxylactams (7a-c). To a stirred solution of **6a** (3.1 g, 11.4 mmol) in 40 mL of THF was added DIBAL-H (1M in THF solution, 22.9 mL, 22.9 mmol) dropwise at -78 °C and the reaction mixture was allowed to warm to 0 °C. After quenching with aqueous NH_4Cl solution, the reaction mixture was filtered through a pad of Celite 545 and the filtrate was extracted with EtOAc. The combined extract was dried over $MgSO_4$, concentrated and purified with column chromatography (EtOAc/*n*-hexane = 5 : 1) to afford **7a** (2.15 g, 68%) as a pale yellow oil: IR (KBr) 3376, 2928, 1704, 1578, 1438 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 4.8 Hz, 1H, pyridine C2-H), 7.55 (d, *J* = 7.6 Hz, 1H, pyridine C4-H), 7.24-7.14 (m, 4H, pyridine C2-H, phenyl), 7.01 (d, *J* = 7.6 Hz, 2H, phenyl), 5.26 and 3.95 (ABq, *J* = 16.3 Hz, 2H, pyridine-C$\underline{H}_2$-Ar), 2.70 (m, 1H, O=C-CH$_2$-C$\underline{H}_a$-), 2.29 (m, 1H, O=C-CH$_2$-C$\underline{H}_b$-), 1.87 (m, 1H, -C$\underline{H}_a$-CH$_2$-CH-OH), 1.70 (m, 1H, -C$\underline{H}_b$-CH$_2$-CH-OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 151.0, 146.2, 145.9, 140.6, 139.6, 133.3, 128.7, 126.7, 122.8, 85.6, 38.2, 29.6, 27.4.

Preparation of 7b and 8b. Prepared from **6b** (197 mg, 0.7 mmol) as described above: **7b** (29 mg, 15%) as a yellow solid; mp 94-95 °C; IR (KBr) 3335, 2947, 2366, 1624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 4.8, 1.6 Hz, 1H, pyridine C2-H), 7.51 (dd, *J* = 7.6, 1.0 Hz, 1H, pyridine C4-H), 7.24-7.10 (m, 5H, phenyl), 6.94 (d, *J* = 7.0 Hz, 1H, pyridine C3-H), 4.77 (t, *J* = 2.6 Hz, 1H, -N-C$\underline{H}$(OH)-CH$_2$-) 3.90 and 3.79 (ABq, *J* = 16.2 Hz, 2H, pyridine-C$\underline{H}_2$-Ar), 2.46 (dd, *J* = 11.3, 1.4 Hz, 1H, O=C-C$\underline{H}$a-), 2.27-2.21 (m, 2H, O=C-CH$_2$-C$\underline{H}_2$-), 1.72 (dd, *J* = 12.2, 2.0 Hz, 1H, O=C-C$\underline{H}_b$-), 1.57 (m, 1H, -N-CH(OH)-C$\underline{H}_a$-), 1.01 (m, 1H, -N-CH(OH)-C$\underline{H}_b$-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 155.1, 146.4, 140.6, 140.0, 134.2, 129.0, 128.8, 126.9, 123.3, 82.2, 38.6, 33.1, 28.5, 16.6. **8b** (over-reduced product, 59 mg, 30%) as a yellow solid; mp 104 °C; IR (KBr) 3334, 3186, 2937, 1722, 1656 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 3.3 Hz, 1H, pyridine C2-H), 7.46 (d, *J* = 7.5 Hz, 1H, pyridine C4-H), 7.28-7.21 (m, 5H, phenyl), 7.10 (t, *J* = 3.8 Hz, 1H, pyridine C3-H), 4.00 (s, 2H, pyridine-C$\underline{H}_2$-Ar), 3.58 (t, *J* = 6.2 Hz, 2H, -NH-CO-C$\underline{H}_2$-) 2.41 (t, *J* = 7.2 Hz, 2H, HO-C$\underline{H}_2$-CH$_2$-), 1.80-1.70 (m, 2H, HO-CH$_2$-C$\underline{H}_2$-), 1.61-1.54 (m, 2H, O=C-CH$_2$-C$\underline{H}_2$-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 149.8, 146.2, 140.2 139.3, 129.5, 129.0, 126.9, 122.3, 62.2, 37.9, 36.3, 32.336, 22.041 397, 174.0, 151.0, 146.2, 145.9, 140.6, 139.6, 133.3, 128.7, 126.7, 122.8, 85.6, 38.2, 29.6, 27.4.

Preparation of 7c and 8c. Prepared from **6c** (1.05 g, 3.7 mmol) as described above: **7c** (211 mg, 20%) as a white solid; mp 129-131 °C; IR (KBr) 3274, 2972, 1654, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.0 Hz, 1H, pyridine C2-H), 7.68 (d, *J* = 5.9 Hz, 1H, pyridine C4-H), 7.31-7.20 (m, 5H, phenyl), 7.02 (s, 1H, pyridine C3-H), 5.96 (s, 1H, -N-C$\underline{H}$(OH)-CH$_2$-) 4.31 (d, *J* = 16.4 Hz, 1H, O=C-C$\underline{H}_a$-O-), 4.13-3.91 (m, 3H, O=C-C$\underline{H}_b$-O-, -N-CH(OH)-C$\underline{H}_2$-), 3.76 and 2.86 (ABq, *J* = 11.9 Hz, 2H, pyridine-C$\underline{H}_2$-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 146.6, 141.1, 139.7, 134.1, 129.0, 128.0, 127.1, 123.7, 103.3, 80.0, 67.9, 67.4, 31.1. **8c** (over-reduced product, 140 mg, 13%) as a brown oil; IR (KBr) 3385, 2960, 2368, 1748, 1700, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.81 (br, 1H, -N$\underline{H}$), 8.37 (d, *J* = 4.7 Hz, 1H, pyridine C2-H), 7.48 (d, *J* = 7.7 Hz, 1H, pyridine C4-H), 7.31-7.22 (m, 5H, phenyl), 7.13 (d, *J* = 6.5 Hz, 1H, pyridine C3-H), 4.20 (s, 2H, -NH-CO-C$\underline{H}_2$-O-), 4.10 (m, 2H, -O-C$\underline{H}_2$-CH$_2$-OH), 4.02 (-O-C$\underline{H}_2$-CH$_2$-OH) 3.97 and 3.95(ABq, *J* = 8.1 Hz, pyridine-C$\underline{H}_2$-Ar).

Preparation of 7d and 8d. Prepared from **6d** (208 mg, 0.7 mmol) as described above: hydroxylactam **7d** (41 mg, 20%) as a colorless oil; IR (KBr) 2924, 2362, 1730, 1646, 1581 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.4 Hz, 1H, pyridine C2-H), 7.68 (d, *J* = 7.7 Hz, 1H, pyridine C4-H), 7.35-7.05 (m, 5H, phenyl), 7.02 (d, *J* = 7.5 Hz, 1H, pyridine C3-H), 5.02 (t, *J* = 3.1 Hz, 1H, -N-C$\underline{H}$(OH)-CH$_2$-), 3.97 and 3.90 (ABq, *J* = 14.2 Hz, 2H, pyridine-C$\underline{H}_2$-Ar),

3.38 (s, 2H, O=C-C$\underline{H}_2$-), 2.69 (dd, *J* = 13.7, 2.7 Hz, 1H, -S-C$\underline{H}_a$-CH-OH), 2.31 (dd, *J* = 13.7, 2.8 Hz, 1H, -S-C$\underline{H}_b$-CH-OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 146.3, 140.5, 139.3, 133.9, 129.6, 128.7, 128.4, 123.4, 81.2, 38.1, 30.5, 29.6. **8d** (over-reduced product, 62 mg, 30%) as a brown oil**;** IR (KBr) 3246, 2924, 1730, 1672, 1591 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, *J* = 1.7 Hz, 1H, pyridine C2-H), 7.51 (d, *J* = 7.7 Hz, 1H, pyridine C4-H), 7.33-7.16 (m, 5H, phenyl), 7.12 (d, *J* = 6.7 Hz, 1H, pyridine C3-H), 4.03 (s, 2H, O=C-C$\underline{H}_2$-S), 3.76 (t, *J* = 5.4 Hz, 2H, -CH$_2$-C$\underline{H}_2$-OH), 3.39 (s, 2H, pyridine-C$\underline{H}_2$-Ar), 2.78 (t, *J* = 5.6 Hz, 2H, S-C$\underline{H}_2$-CH$_2$-OH).

General procedure for the conversion of hydroxyamides (8d, 8f) to hydroxylactams (7d, 7f). A solution of over-reduced product, hydroxyamide **8d** (100 mg, 0.3 mmol) in 10 mL of distilled DMSO was treated with triethylamine (0.276 mL, 1.98 mmol) and the mixture was stirred for 40 min at room temperature. A solution of pyridine-SO_3 complex (158 mg, 0.99 mmol) in 10 mL of DMSO was added into the above mixture. The reaction mixture was stirred for 2 h at room temperature and treated with a mixture of water and EtOAc. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The resultant residue was purified with column chromatography (EtOAc/*n*-hexane = 2 : 1) to provide **7d** (68 mg, 69%) as a colorless oil.

Preparation of 7f. The reaction of **6f** (263 mg, 0.9 mmol) as described above afforded hydroxyamide **8f** (88 mg, 33%) as a white solid; mp 88 °C; IR (KBr) 3348, 3238, 2898, 1660, 1586, 1518 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 4.8, 1.8 Hz, 1H, pyridine C2-H), 7.57 (dd, *J* = 7.6, 2.0 Hz, 1H, pyridine C4-H), 7.18-7.12 (m, 2H, thienyl C3,5-H) 6.94 (dd, *J* = 5.1, 3.4 Hz, 1H, thienyl C4-H), 6.81 (d, *J* = 4.4 Hz, 1H, pyridine C3-H), 4.18 (s, 2H, pyridine-C$\underline{H}_2$-Ar), 3.61 (t, *J* = 6.0 Hz, 2H, O=C-C$\underline{H}_2$-), 2.46 (t, *J* = 7.1 Hz, 2H, -C$\underline{H}_2$-OH), 1.81-1.57 (m, 4H, O=C-CH$_2$-C$\underline{H}_2$-C$\underline{H}_2$-). Compound **8f** was converted into hydroxylactam **7f** as a yellow oil in 74% yield by the above Parikh oxidation reaction: IR (KBr) 3435, 2926, 2362, 1666, 1631 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 4.8, 1.7 Hz, 1H, pyridine C2-H), 7.62 (d, *J* = 9.2 Hz, 1H, pyridine C4-H), 7.26-7.21 (m, 1H, thienyl C3-H), 7.12 (d, *J* = 4.8 Hz, 1H, thienyl C5-H), 6.91 (dd, *J* = 5.2, 3.4 Hz, 1H, thienyl C4-H), 6.73 (d, *J* = 3.0 Hz, 1H, pyridine C3-H), 5.03 (t, *J* = 2.5 Hz, 1H, -N-C$\underline{H}$-OH), 4.19 and 3.96 (ABq, *J* = 16.5 Hz, 2H, pyridine-C$\underline{H}_2$-Ar), 2.54-2.36 (m, 2H, O=C-C$\underline{H}_2$-), 1.93-1.70 (m, 2H, O=C-CH$_2$-CH$_2$-C$\underline{H}_2$-), 1.42-1.33 (m, 2H, O=C-CH$_2$-C$\underline{H}_2$-).

General procedure for *N*-acyliminium ion cyclization (9a-d, 9f). The reaction mixture of **7a** (115 mg, 0.43 mmol) and 1 mL of *conc.* H_2SO_4 was stirred for 2 h at room temperature and treated with aqueous $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, concentrated and purified with column chromatography (EtOAc/*n*-hexane = 5 : 1) to provide **9a** (48 mg, 45%) as a yellow solid: mp 175-176 °C; IR (KBr) 3395, 2368, 1706, 1586 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.9, 1.8 Hz, 1H, pyridine C2-H), 7.65 (d, *J* = 9.3 Hz, 1H, pyridine C4-H), 7.26-7.15 (m, 4H, phenyl), 7.10 (t, *J* = 7.1 Hz, 1H, pyridine C3-H), 5.17 (dd, *J* = 9.4, 6.4 Hz, 1H, -N-C$\underline{H}$-Ar-), 4.46 and 3.50 (ABq, *J* = 14.3 Hz, 2H, pyridine-C$\underline{H}_2$-Ar), 2.73-2.61 (m, 3H, O=C-C$\underline{H}_2$-CH$_2$-, O=C-CH$_2$-C$\underline{H}_a$-), 2.21 (m, 1H, O=C-CH$_2$-C$\underline{H}_b$-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 148.5, 138.5, 137.1, 134.7, 130.4, 128.2, 127.9, 123.7, 118.2, 111.9, 111.7, 62.3, 38.1, 31.4, 31.2.

Preparation of 9b. Prepared from **7b** (29 mg, 0.10 mmol) as described above: **9b** (16 mg, 60%) as a white solid; mp 134-137 °C; MS *m*/*z*: 264 (M^+); IR (KBr) 3415, 2927, 2378, 1668, 1586 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.8 Hz, 1H, pyridine C2-H), 7.61 (d, *J* = 7.4 Hz, 1H, pyridine C4-H), 7.18-7.08 (m, 5H, pyridine C3-H, phenyl), 5.06 (t, *J* = 5.1 Hz, 1H, -N-C$\underline{H}$-Ar-) 4.52 and 3.42 (ABq, *J* = 14.3 Hz, 2H, pyridine-C$\underline{H}_2$-Ar), 2.75-2.59 (m, 2H, O=C-C$\underline{H}_2$-CH$_2$-), 2.44-2.16 (m, 2H, O=C-CH$_2$-C$\underline{H}_2$-), 2.03-1.85 (m, 2H, -N-CH-C$\underline{H}_2$-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 148.5, 148.3, 139.0, 136.8, 136.4, 136.2, 130.2, 128.4, 127.5, 127.4, 123.8, 61.2, 38.2, 33.4, 33.0, 19.3.

Preparation of 9c. Prepared from **7c** (39 mg, 0.14 mmol) as described above: **9c** (23 mg, 63%) as a white solid: mp 209-211 °C; MS *m*/*z*: 266 (M^+); IR (KBr) 3408, 2388, 1664, 1578 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.8 Hz, 1H, pyridine C2-H), 7.65 (d, *J* = 7.6 Hz, 1H, pyridine C4-H), 7.26-7.16 (m, 4H, phenyl), 7.06 (d, *J* = 7.3 Hz, 1H, pyridine C3-H), 5.28 (dd, *J* = 8.8, 4.0 Hz, 1H, -N-C$\underline{H}$-Ar-) 4.56 and 3.45 (ABq, *J* = 14.2 Hz, 2H, pyridine-C$\underline{H}_2$-Ar), 4.54 and 4.39 (ABq, *J* = 17.1 Hz, 2H, O=C-C$\underline{H}_2$-), 4.24 (dd, *J* = 12.2, 4.4 Hz, 1H, -N-CH(Ar)-C$\underline{H}_a$-), 3.93 (dd, *J* = 12.2, 9.0 Hz, 1H, -N-CH(Ar)-C$\underline{H}_b$-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 151.0, 148.7, 137.3, 136.7, 133.4, 130.4, 129.0, 128.4, 127.9, 124.4, 71.2, 69.1, 60.6, 37.9.

Preparation of 9d. Prepared from **7d** (80 mg, 0.27 mmol) as described above: **9d** (56 mg, 70%) as a white solid; mp 109-110 °C; MS *m*/*z*: 282 (M^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 8.7, 4.3 Hz, 1H, pyridine C2-H), 8.20 (d, *J* = 7.0 Hz, 1H, pyridine C4-H), 7.61 (dd, *J* = 13.4, 5.8 Hz, 1H, phenyl C3-H), 7.31-7.19 (m, 5H, phenyl) 5.53 (t, *J* = 6.0 Hz, 1H, -N-C$\underline{H}$-Ar-) 4.61 and 3.71 (ABq, *J* = 14.3 Hz, 2H, O=C-C$\underline{H}_2$-S-), 4.12 and 3.47 (ABq, *J* = 15.5 Hz, 2H, pyridine-C$\underline{H}_2$-Ar), 3.36 (d, *J* = 6.6 Hz, 2H, -N-CH(Ar)-C$\underline{H}_2$-).

Preparation of 9f. Prepared from **7f** (94 mg, 0.33 mmol) and methanesulfonic acid (0.211 mL, 3.26 mmol) as described above: **9f** (27 mg, 31%) as a white solid: mp 195-197 °C; MS *m*/*z*: 270 (M^+); IR (KBr) 3405, 2926, 2857, 1646 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 5.0, 1.7 Hz, 1H, pyridine C2-H), 7.64 (dd, *J* = 7.5, 1.5 Hz, 1H, pyridine C4-H), 7.26-7.20 (m, 1H, pyridine C3-H), 7.05 (d, *J* = 5.3 Hz, 1H, thienyl C5-H), 6.77 (d, *J* = 5.3 Hz, 1H, thienyl C4-H), 4.91 (s, 1H, -N-C$\underline{H}$-Ar), 4.36 and 3.63 (ABq, *J* = 16.2 Hz, 2H, pyridine-C$\underline{H}_2$-Ar), 2.63-2.57 (m, 2H, O=C-C$\underline{H}_2$-), 2.43-2.34 (m, 2H, -N-CH(Ar)-C$\underline{H}_2$-), 1.92-1.76 (m, 2H, O=C-CH$_2$-C$\underline{H}_2$-).

General procedure for the preparation of pyridoazepines (4a-d, 4f). To a solution of **9a** (67 mg, 0.27 mmol) in 10 mL of THF was added $BF_3{\cdot}OEt_2$ solution (1 M

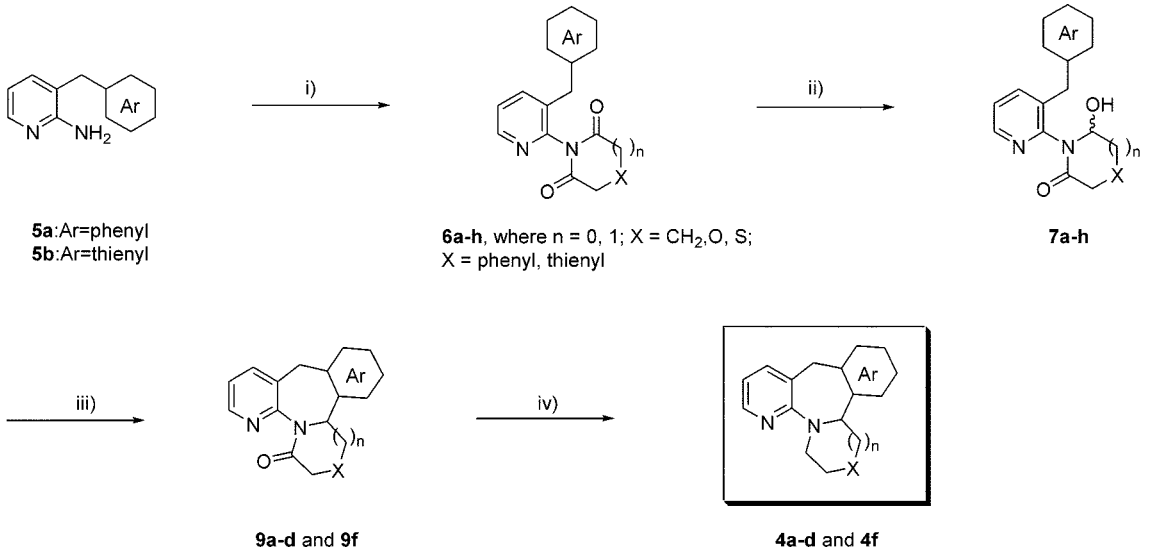
solution in THF, 0.47 mL, 0.47 mmol) at 0 °C, and the mixture was stirred for 30 min at and treated with $BH_3 \cdot SMe_2$ (2 M solution in THF, 0.2 mL, 0.4 mmol). After stirring for 3 h at room temperature, the reaction mixture was treated with 1 N HCl solution followed by an addition of mixture of water and EtOAc. The separated organic layer was dried over $MgSO_4$, concentrated and purified with column chromatography (EtOAc/*n*-hexane = 1 : 5) to afford **4a** (37 mg, 60%) as a white solid: mp 113-115 °C; MS *m/z*: 236 (M^+); IR (KBr) 2952, 2856, 1588, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 4.8, 0.9 Hz, 1H, pyridine C2-H), 7.32-7.25 (m, 4H, pyridine C4-H, phenyl), 7.17 (d, *J* = 7.2 Hz, 1H, phenyl) 6.40 (dd, *J* = 7.2, 5.1 Hz, 1H, pyridine C3-H), 5.60 (t, *J* = 6.3 Hz, 1H, N-C<u>H</u>-phenyl), 4.89 and 3.38 (ABq, *J* = 14.7 Hz, 2H, Ar-C<u>H</u>$_2$-phenyl), 3.71 (t, *J* = 6.6 Hz, 2H, N-C<u>H</u>$_2$-), 2.59 (m, 1H, N-CH-C<u>H</u>$_a$-), 2.33 (m, 1H, N-CH-C<u>H</u>$_b$-), 2.10 (m, 2H, N-CH_2-C<u>H</u>$_2$-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 139.9, 138.0, 136.6, 128.3, 128.0, 127.3, 123.7, 123.7, 118.2, 111.9, 111.7, 57.8, 49.6, 39.8, 30.1, 23.6.

Preparation of 4b. Prepared from **9b** (84 mg, 0.317 mmol) as described above: **4b** (64 mg, 80%) as a white solid; mp 80 °C; MS *m/z*: 250 (M^+); IR (KBr) 3425, 2924, 2827, 2378, 1586 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 5.0 Hz, 1H, pyridine C2-H), 7.28 (d, *J* = 7.1 Hz, 1H, pyridine C4-H), 7.12-6.98 (m, 4H, phenyl), 6.68 (dd, *J* = 7.1, 5.1 Hz, 1H, pyridine C3-H), 4.55 and 3.34 (ABq, *J* = 13.1 Hz, 2H, pyridine-C<u>H</u>$_2$-Ar), 4.12 (d, *J* = 10.3 Hz, 1H, -N-C<u>H</u>$_a$-CH_2-), 3.96 (d, *J* = 12.1 Hz, 1H, N-C<u>H</u>$_b$-CH_2-), 3.13 (t, *J* = 12.1 Hz, 2H, -N-C<u>H</u>$_2$-Ar), 2.01-1.94 (m, 2H, -N-CH(Ar)-C<u>H</u>$_2$-), 1.85-1.67 (m, 4H, -N-CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 146.2, 140.4, 138.0, 134.2, 132.5, 129.7, 127.9, 127.2, 116.8, 116.6, 67.8, 51.1, 38.6, 38.5, 38.3, 26.8.

Preparation of 4c. Prepared from **9c** (24 mg, 0.09 mmol) as described above: **4c** (10 mg, 44%) as a white solid: mp 97-100 °C; MS *m/z*: 252 (M^+); IR (KBr) 3415, 2976, 2857, 2366, 1591 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 3.3 Hz, 1H, pyridine C2-H), 7.35 (d, *J* = 6.6 Hz, 1H, pyridine C4-H), 7.18-7.10 (m, 4H, phenyl), 6.77 (dd, *J* = 7.2, 5.1 Hz, 1H, pyridine C3-H), 4.54 and 3.49 (ABq, *J* = 13.7 Hz, 1H, pyridine-C<u>H</u>$_2$-Ar), 4.38 (d, *J* = 7.2 Hz, 1H, -N-C<u>H</u>-phenyl), 4.05 (dt, *J* = 11.0, 2.7 Hz, 1H, -N-CH_2-C<u>H</u>$_a$-O-), 3.89-3.80 (m, 3H, -N-CH_2-C<u>H</u>$_b$-O-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 146.2, 140.4, 135.0, 131.2, 129.4, 128.2, 127.6, 127.0, 117.8, 116.6, 73.5, 67.6, 64.8, 49.0, 38.3.

Preparation of 4d. Prepared from **9d** (56 mg, 0.20 mmol) as described above: **4d** (16 mg, 30%) as a yellow solid: mp 106 °C; MS *m/z*: 268 (M^+); IR (KBr) 3415, 2917, 2837, 2366, 1725, 1574 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 4.9 Hz, 1H, pyridine C2-H), 7.39 (d, *J* = 7.1 Hz, 1H, pyridine C4-H), 7.23-7.12 (m, 5H, phenyl), 6.72 (dd, *J* = 7.0, 5.0 Hz, 1H, pyridine C3-H), 4.50 (d, *J* = 10.4 Hz, 1H, -N-C<u>H</u>- Ar), 4.37 (m, 1H, N-C<u>H</u>$_a$), 4.35 and 3.53 (ABq, *J* = 13.2 Hz, 2H, pyridine-C<u>H</u>$_2$-Ar), 3.33 (m, 1H, N-C<u>H</u>$_a$), 2.90 (m, 1H, S-C<u>H</u>$_a$-CH-Ph), 2.62 (m, 1H, S-C<u>H</u>$_b$-CH-Ph), 2.44 (m, 2H, N-CH_2-C<u>H</u>$_2$-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 140.4, 139.2, 136.7, 136.6, 132.5, 129.5, 129.4, 129.2, 128.7, 128.3, 116.4, 68.5, 54.3, 38.4, 35.0, 27.9.

Preparation of 4f. Prepared from **9f** (30 mg, 0.11 mmol) as described above: **4f** (5 mg, 21%) as a yellow solid; mp 108-111 °C; MS *m/z*: 256 (M^+); IR (KBr) 3420, 2930, 2840, 1578, 1432 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 4.9 Hz, 1H, pyridine C2-H), 7.29 (d, *J* = 7.1 Hz, 1H, pyridine C4-H), 6.89 (d, *J* = 5.1 Hz, 1H, thienyl C2-H), 6.75 (dd, *J* = 7.1, 5.0 Hz, 1H, pyridine C3-H), 6.66 (d, *J* = 5.1 Hz, 1H, thienyl C3-H), 4.47 and 3.40 (ABq, *J* = 14.5 Hz, 2H, pyridine-C<u>H</u>$_2$-Ar), 4.05 (d, *J* = 11.5 Hz, 1H, -N-C<u>H</u>-Ar), 3.70 (m, 1H, -N-C<u>H</u>$_a$-CH_2-), 3.20 (m, 1H, -N-C<u>H</u>$_b$-CH_2-), 1.95-1.59 (m, 6H, -N-CH-C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 146.3, 138.7, 134.0, 133.6, 128.8,



Scheme 1. [a]Reagents: i) succinic anhydride (n=0), glutaric anhydride (n=1), diglycolic anhydride (n=1, X=O), thiodiglycolic acid (n=1, X=S), AcCl, xylene, reflux; ii) DIBAL-H, THF, -78 °C; iii) *conc*. H_2SO_4 (**7a-d**) or CH_3SO_3H (**7e-f**, **7h**), rt; iv) $BF_3 \cdot OEt_2$ and $BH_3 \cdot SMe_2$, THF, rt.

121.2, 117.6, 117.4, 64.1, 51.7, 37.5, 31.5, 26.5, 25.7.

Results and Discussion

As shown in Scheme 1, our basic strategy utilizes the *N*-acyliminium ion cyclization of hydroxylactam **7a-h** with aromatic ring as π-nucleophile under the acidic condition.[6] As a first step, 2-amino-3-phenylmethylpyridines (**5a**) and 2-amino-3-thienylmethylpyridine (**5b**), which were prepared by known procedure,[7] were condensed with various anhydrides or dicarboxylic acids to afford the cyclic imides **6a-h** in moderate to good yields (38-75%). The results of all reactions were summarized in Table 1.

In case of the reduction of cyclic imides to hydroxylactams with $NaBH_4$, the hydroxyamides **8**, over-reduced compounds, were obtained predominantly instead of the desired hydroxylactams consistent with our previous results.[5] Other reducing agents such as Red-Al and bis(2,6-dimethoxyphenoxy)borane (BDMPB) also gave the side-products.[8] On the other hand, the reduction of cyclic imides **6a-h** with DIBAL-H provided hydroxylactams **7** along with hydroxyamides (**8**) in various ratios depending on the substrates. 2-Thienyl derivatives **6f-h** were, however, transformed to hydroxyamides **8f-h**. Fortunately, these over-reduced compounds **8d**, **8f** and **8h** could be cleanly converted into the desired hydroxylactams in acceptable yield by Parikh oxidation (Pyr.-SO_3 complex).[9] The results of these reactions were summarized in Table 2.

The hydroxylactams **7a-f** and **7h** were subjected to the acidic condition of *N*-acyliminium ion cyclization to obtain tetracyclic ring system. The hydroxylactams **7a-d**, which have a phenyl ring as a π-nucleophile were cyclized smoothly on treatment of *conc.* H_2SO_4 to afford the cyclized products in 45-70% yields. However, the cyclization of hydroxylactams **7e** and **7h**, which have a thienyl ring as a π-nucleophile, did not take place on the various *N*-acyliminium ion cyclization conditions. The hydroxylactam **7f** was only cyclized successfully on treatment of CH_3SO_3H as an activator to afford the cyclized product **9f** in 31% yield.[10] This may due to the instability of thienyl ring on the vigorous acidic cyclization conditions. Finally, the reduction of lactam carbonyl group in **9a-d** and **9f** with $BH_3 \cdot SMe_2$ in the presence of $BF_3 \cdot OEt_2$ provided tetracyclic pyrido[2,3-*b*]azepines **4a-d**, and **4f** in 31-80% yields, respectively.

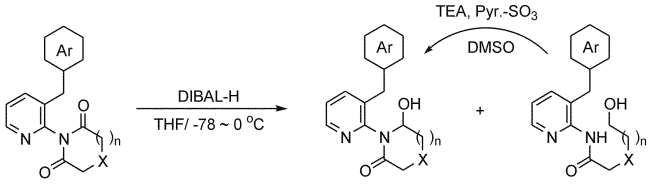
For the evaluation of biological effect of synthetic compounds as well as our previously reported compounds,[5] the binding assay for α_2-adrenoceptor was performed according to the previously reported method and summarized in Table

Table 1. Structures and yields of each reaction in Scheme 1

Entry	Ar	n	X	Yield of **6** (%)[a]	Yield of **9** (%)[a]	Yield of **4** (%)[a]
a	Phenyl	0	CH_2	75	45	60
b	Phenyl	1	CH_2	38	60	80
c	Phenyl	1	O	41	63	44
d	Phenyl	1	S	47	70	30
e	2-Thienyl	0	CH_2	63	decom.[b]	–
f	2-Thienyl	1	CH_2	70	31[b]	31
g	2-Thienyl	1	O	52	–	–
h	2-Thienyl	1	S	60	decom.[b]	–

[a]Isolated yield. [b]CH_3SO_3H was used for cyclization instead of *conc.* H_2SO_4.

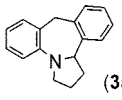
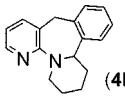
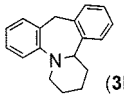
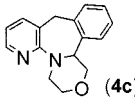
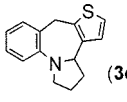
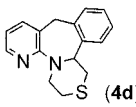
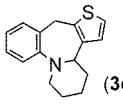
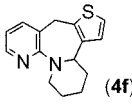
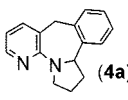
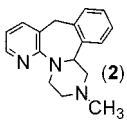
Table 2. Reduction of cyclic imides (**6a-h**) and Parikh oxidation of the corresponding over-reduced compounds (**8d**, **8f**, and **8h**) to hydroxylactams (**7a**, **7f**, and **7h**)



Entry	Ar	n	X	Yield of **7** (%)[a]	Ratio (**7** : **8**)[a]	Yield of **7** from **8** (%)[b]
a	Phenyl	0	CH_2	68	1 : 0	–
b	Phenyl	1	CH_2	15	1 : 2	decom.
c	Phenyl	1	O	20	3 : 2	–[d]
d	Phenyl	1	S	40[c]	2 : 3	69
e	2-Thienyl	0	CH_2	65	6 : 1	–[d]
f	2-Thienyl	1	CH_2	24[c]	0 : 1	74
g	2-Thienyl	1	O	–	0 : 1	decom.
h	2-Thienyl	1	S	25[c]	0 : 1	60

[a]Isolated yield. [b]Isolated ratio of **7** and **8**. [c]Combined yield (reduction and oxidation). [d]Not tried.

Table 3. The binding affinity of synthetic compounds for α_2-adrenoceptor

No.	Structure	*K*i (μM)[a]	No.	Structure	*K*i (μM)[a]
1[b]	 (**3a**)	1.03	6	 (**4b**)	>10
2[b]	 (**3b**)	>10	7	 (**4c**)	>10
3[b]	 (**3c**)	2.22	8	 (**4d**)	>10
4[b]	 (**3d**)	>10	9	 (**4f**)	2.73
5	 (**4a**)	0.26	10[c]	 (**2**)	0.08

[a]Affinities of compounds were determined using competition binding assay in the presence of 1 nM of [^{3}H]rauwolscine. [b]Compounds from the previous results[ref.5]. [c]Mirtazapine (**2**) was prepared by the known procedure.[ref.4]

3.[11] The binding affinity data of mirtazapine (**2**) was also inserted for activity comparison. In general, tetracyclic azepins **3a**, **3c**, and **4a**, which have a five-membered pyrrolidine ring showed better binding affinities than other tetracyclic azepines having a six-membered piperidine, morpholine or thiomorpholine ring. Among tested compounds, 2,3,9,13b-tetrahydro-1*H*-benzo[*f*]pyrrolo[2,1-*a*]pyrido[2,3-*c*]azepine (**4a**) was the most potent (Ki = 0.26 μM) but showed about 3-fold less binding affinity than mirtazapine (**2**) (Ki = 0.08 μM) for α_2-adrenoceptor. On the other hand, tetracyclic azepines having a six-membered ring showed no noticeable binding affinities except compound **4f** (Ki = 2.73 μM).

In conclusion, tetracyclic pyrido[2,3-*b*]azepine derivatives (**4a**-**d** and **4f**) were successfully synthesized as analogues of mirtazapine through *N*-acyliminium ion cyclization strategy starting from 2-amino-3-arylmethylpyrines **5a** and **5b**. The key intermediates, hydroxylactams **7**, were prepared by reduction of the corresponding imides with only DIBAL-H followed by Parikh oxidation of the resulting over-reduced compounds **8**. The α_2-adrenoceptor binding affinity data of synthetic compounds showed that 4-methyl group of piperazine moiety of mirtazapine plays an important role for the binding affinity for α_2-adrenoceptor.

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References

1. (a) Roeder, T.; Degen, J.; Gewecke, M. *Eur. J. Pharmacol.* **1998**, *349*, 171-177. (b) Briel, D. *Pharmazie.* **1990**, *45*, 895-899.
2. (a) De Boer, T.; Nefkens, F.; Van Helvoirt, A. *Eur. J. Pharmacol*. **1994**, *253*, R5-R6. (b) De Boer, T.; Nefkens, F.; Van Helvoirt, A.; Van Delft, A. M. L. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 852-860. (c) Haddjeri, N.; Blier, P.; De Montigny, C. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 861-871.
3. (a) Nickolson, V. J.; Wieringa, J. H. *J. Pharm. Pharmacol.* **1981**, *33*, 760-766. (b) Wood, M. D.; Thomas, D. R. Watkins, C. J.; Newberry, N. R. *J. Pharm. Pharmacol.* **1993**, *45*, 711-714. (c) Pinder, R. M.; Van Delft, A. M. L. *Br. J. Clin. Pharmacol*. **1983**, *15*, 269S-276S.
4. (a) Berger, J. G.; Chang, W. K.; Clader, J. W.; Hou, D.; Chipken, R. E.; McPhail, A. T. *J. Med. Chem*. **1989**, *32*, 1913-1921. (b) Draper, R. W.; Hou, D.; Iyer, R.; Lee, G. M.; Liang, J. T.; Mas, J. L.; Tormos, W.; Vater, E. J.; Gunter, F.; Mergelsberg, I.; Scherer, D. *Org. Process Res. Dev.* **1998**, *2*, 175-185. (c) Reinhard, R.; Glaser, M.; Neumann, R.; Maas, G. *J. Org. Chem.* **1997**, *62*, 7744-7751. (d) McKenna, M. T.; Proctor, G. R.; Young, L. C.; Harvey, A. L. *J. Med. Chem.* **1997**, *40*, 3516-3523. (e) Lee, Y. S.; Min, B. J.; Park, Y. K.; Lee, J. Y.; Lee, S. J.; Park, H. *Tetrahedron Lett.* **1999**, *40*, 5569-5572.
5. Lee, J. Y.; Baek, N. J.; Lee, S. J.; Park, H.; Lee, Y. S. *Heterocycles* **2001**, *55*, 1519-1526.
6. (a) Kim, J. H.; Lee, Y. S.; Park, H.; Kim, C. S. *Tetrahedron* **1998**, *54*, 7395-7400. (b) Tanis, S. P.; Deaton, M. V.; Dixon, L. A.; McMills, M. C.; Raggon, J. W.; Collins, M. A. *J. Org. Chem*. **1998**, *63*, 6914-6928.
7. Kametani, S.; Surgenor, A.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* **1981**, 920-925.
8. (a) Kang, J.; Lee, J. W.; Kim, J. I.; Pyun, C. *Tetrahedron Lett*. **1995**, *36*, 4265-4268. (b) Kang, J.; Lee, C. W.; Lim, G. J.; Cho, B. T. *Tetrahedron: Asymmetry* **1999**, *10*, 657-660.
9. Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.
10. Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 173-178.
11. Chung, S.-H.; Yook, J.; Min, B. J.; Lee, J. Y.; Lee, Y. S.; Jin, C. *Arch. Pharm. Res.* **2000**, *23*, 353-359.