Rapid Synthesis of Arylpiperazine Derivatives for Imaging 5-HT$_{1A}$ Receptor under Microwave Irradiation

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We have established an efficient method for the synthesis of the arylpiperazine derivatives in which the acylation of 2-aminopyridine, the coupling reaction of the acyl compound with piperazines, and reduction of the arylpiperazines were performed under a microwave irradiation (300 W) to afford the corresponding target compounds in quantitative yields. In all cases, the reaction times were remarkably reduced when compared with those of the conventional method.

Key Words : Arylpiperazines, Serotonin receptors, Microwave irradiation

Introduction

The serotonergic system, with its different receptor subtypes, is one of the most important neurotransmitter systems in the brain and it is involved in the regulation of various physiological functions and the state of the mind.[1] The receptors that are activated by 5-HT have been divided into at least seven classes (5-HT$_{1-7}$), and each class has been further subdivided into different subtypes (A, B...).[2] One of the serotonin receptor subtypes, 5-HT$_{1A}$, plays an important function as the somatodendritic autoreceptor (presynaptic) in the dorsal raphe nucleus and as a postsynaptic receptor for 5-HT in the terminal field areas. A large number of agonists and antagonists for 5-HT$_{1A}$ receptors are reported in the literature.[3] An arylpiperazine, WAY100635, has been found as a highly selective ligand for imaging 5-HT$_{1A}$ receptor among other serotonergic receptors.[4]

WAY100635 derivatives **4a-4e** were prepared by the acylation of 2-aminopyridine, the coupling reaction of the acyl compound with piperazines and the reduction of the arylpiperazines (Figure 1). Although most of the conventional methods are useful for the synthesis of these derivatives, a more convenient and efficient method is needed to overcome the problems in these methods which involve large amounts of solvent, long reaction times, especially, in the use of K_2CO_3,[5] and low yields to complete this reaction. In recent years, there has been a gradual change from traditional reaction conditions to more environmentally friendly routes. This growth of green chemistry holds significant potential for a reduction of the by-products, a reduction in waste production and a lowering of the energy costs. Owing to its ability to couple directly with the reacting molecules and bypassing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic synthesis.[6] The most evident improvements are shorter reaction times, higher yields, easier work-up and cleaner reactions due to fewer side reactions than a conventional heating.[7] In this respect, we

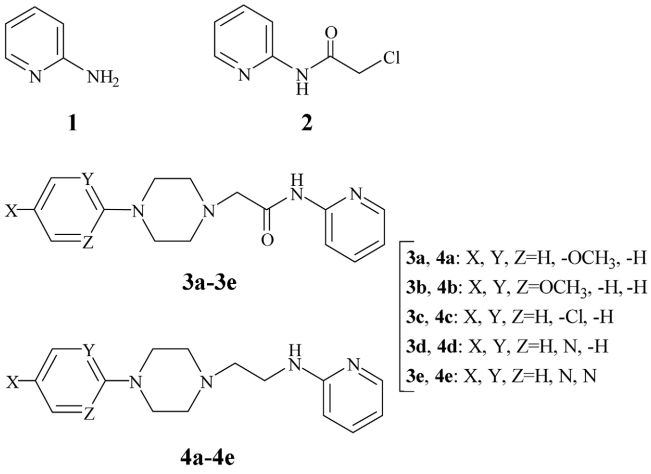


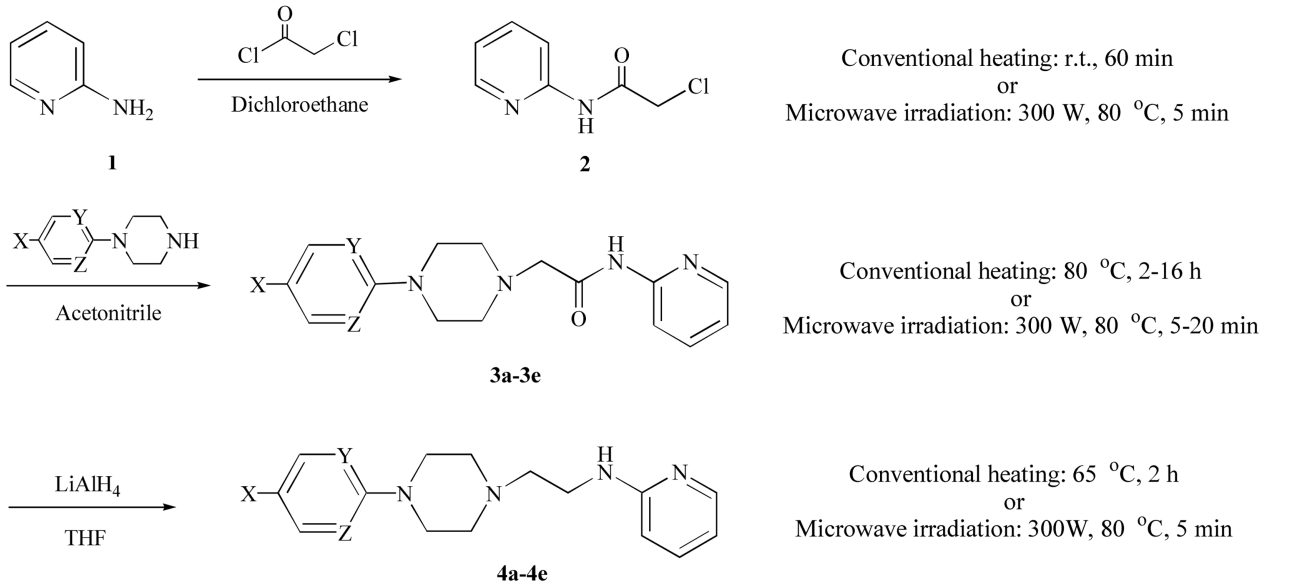
Figure 1. Synthetic sequences leading to WAY100635 derivatives **4a-4e**.

have focused our attention on replacing conventional heating with microwave irradiation (MWI) for the construction of a combinatorial library as well as the faster synthesis, since knowledge of the structural features which influence biological deposition is essential in the design of organ-imaging radiopharmaceuticals.

We herein report a fast, simple, and efficient procedure for the synthesis of the arylpiperazine derivatives using microwave irradiation method.

Results and Discussion

In order to prepare the WAY100635 derivatives in a faster and more efficient way, we envisioned to perform the synthesis of the desired compounds in a microwave-assisted organic synthesizer. The comparative strategy for the synthesis of the compounds (**2**, **3a-3e**, **4a-4e**) using both a microwave irradiation and a conventional heating is summarized in Scheme 1. All of the reactions were carried out both under microwave as well as thermal conditions. The



Scheme 1. Preparation of 2-(chloroacetyl)amidopyridine (**2**), 2-(1,4-arylpiperazinyl)-*N*-(2-pyridyl)acetamide (**3a-3e**) and 1-(aryl)-4-(2-(2-pyridylamino)ethyl)piperazine (**4a-4e**).

synthesis of the WAY100635 derivatives started from the commercially available corresponding 2-aminopyridine. Treatment of 2-aminopyridine with 1.1 equivalence of chloroacetyl chloride gave the corresponding 2-(chloroacetyl)amidopyridine **2** as a mother moiety. Reaction between the mother moiety and 1.0 equivalence of arylalkylpiperazines, respectively in the presence of K_2CO_3 gave the corresponding piperazines **3a-3e**, which were reduced by $LiAlH_4$ in THF to provide the desired compounds **4a-4e**. All the products were isolated easily by column chromatography or recrystallization and they provided satisfactory instrumental analysis results.

The reaction temperature under microwave was controlled and monitored using a pulsed irradiation system and the temperature was measured after each pulse. The enhancement of the reaction rate and yield can be attributed to the absorption of more microwave energy by the polar reactants, which generates sufficient heat energy to promote the reaction.

In general, 300 W, 1 min and 130 °C of microwave irradiation conditions were applied to the corresponding ligands. Next, we applied the optimized conditions to each step to perform the best. As shown in Figure 2, high incorporation yields were observed at 5 min for the **2**, **3a-3b**, and **4a-4e** (97, 81, 75, 92, 80, 78, 65, and 63% yield, respectively). The yield of **3c-3e** increased with the irradiation time up to 20 min (87, 72, and 65% yield, respectively).

All compounds were synthesized under microwave irradiation to afford the corresponding target compounds in short reaction times. The reaction time of 2-(chloroacetyl)-amidopyridine **2** was reduced from 1 h to 5 min and **3a-4e** were reduced from 2-16 h to 5-20 min, respectively, compared with that of the conventional method. Com-

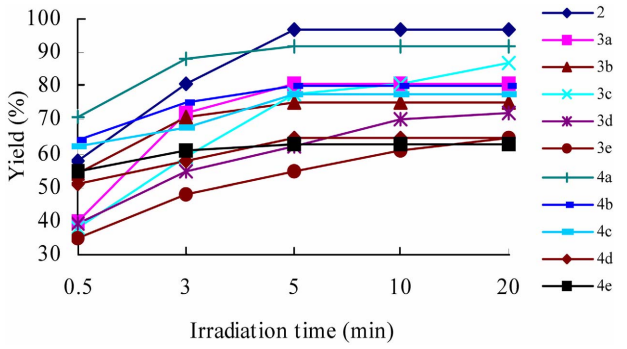


Figure 2. Yields of **2**, **3a-3e** and **4a-4e** using microwave irradiation at 300 W: influence of the irradiation time.

Table 1. Comparison of microwave irradiation method with conventional heating method of sequences for the WAY100635 derivatives

Product	Reaction time		Yield (%)	
	Microwave	Conventional	Microwave	Conventional
2	5 min	1 h	97	90
3a	5 min	2 h	81	73
3b	5 min	16 h	75	68
3c	20 min	16 h	87	72
3d	20 min	16 h	72	42
3e	20 min	16 h	65	58
4a	5 min	2 h	92	75
4b	5 min	2 h	80	53
4c	5 min	2 h	78	48
4d	5 min	2 h	65	45
4e	5 min	2 h	63	55

parative results from both screening experiments are shown in Table 1.

Conclusion

In conclusion, we have developed an efficient method for the synthesis of WAY100635 derivatives **4a-4e** in which the acylation of 2-aminopyridine, the coupling reaction of the acyl compound with piperazines, and the reduction of the arylpiperazines were performed under microwave irradiation to afford the corresponding target compounds in good yields. Despite the usage of heat-sensitive materials such as chloroacetyl chloride and LAH, **4a-4e** can be easily obtained under microwave irradiation allowing for an efficient preparation of libraries of the piperazine derivatives. Considering the reduction of the reaction times and a lowering of the energy costs, this process is economically and environmentally acceptable. This methodology is expected to be applicable to the preparation of radiopharmaceuticals for imaging a neurotransmitter receptor since the resulting compounds are of broad interest as 5-HT$_{1A}$ receptor antagonist.

Experimental Section

General. Unless otherwise stated, all the starting materials were obtained from high-grade commercial suppliers and used without any further purification. The progress of reaction was monitored by TLC analyses, performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm) with a fluorescent indicator (254 nm). Silica gel (Merck 60, size 230-400 mesh) was used for the column chromatography. Melting points were determined on a Mel-Temp (50/60 cycles, 110-120 volts, 250 watts) apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Bomen MB154 FTIR (KBr pellets or neat). ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 300-MHz NMR spectrometer (Korea Basic Science Institute, Daejeon, Korea) in $CDCl_3$ solution, and the chemical shifts were recorded in ppm units using $SiMe_4$ as an internal standard. Mass spectra were measured on a Varian MAT 371 Mass Spectrometer at 70 eV. Microwave irradiation was performed using a Micro-SYNTH with a high-pressure rotor (Milestone, Sorisole, Italy) with a monomodal radiation.

Conventional heating method.

2-(Chloroacetyl)amidopyridine (2): A solution of 2-aminopyridine (2.8 g, 30 mmol) in dichloroethane (25 mL) was placed into an ice bath and stirred for 10 min under nitrogen. Chloroacetyl chloride (2.6 mL, 33 mmol) was added dropwise into the solution, and it was stirred at room temperature for 1 h. After stirring for 1 h, the reaction mixture was adjusted to pH = 9 with a solution of saturated sodium hydroxide in water and extracted two times with dichloroethane. The organic layer was dried over anhydrous sodium sulfate. Removal of the solvent by using a rotary evaporator and recrystallization from acetonitrile gave 4.6 g (90%) of the desired product as a pink solid.

General procedure: 2-(1-4-Arylpiperazinyl)-*N*-(2-pyridyl)acetamide (3a-3e): A solution of arylpipearazines (5.9 mmol) in acetonitrile (5 mL) was added dropwise into a solution of 2-(chloroacetyl)amidopyridine (1.0 g, 6 mmol) and K_2CO_3 (1.6 g, 12 mmol) in acetonitrile (25 mL). The mixture was heated under reflux (80 °C) for about 2 (**3a**) or 16 h (**3b-3e**) and cooled to room temperature. The resulting mixture was dissolved in water, extracted with dichloromethane (two times). The organic layer was washed successively with water and brine, dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product, which was purified by a column chromatography.

2-(1-(4-(2-Methoxyphenyl)piperazinyl))-N-(2-pyridyl)acetamide (3a). The procedure as described above was used with 1.0 mL of 1-(2-methoxyphenyl)pipearazine. Elution with hexane/ethylacetate (8/2) gave 1.4 g (73%) of the desired product as a white solid.

2-(1-(4-(4-Methoxyphenyl)piperazinyl))-N-(2-pyridyl)acetamide (3b). The procedure as described above was used with 1.5 g of 1-(4-methoxyphenyl)piperazine dihydrochloride. Elution with hexane/ethylacetate (8/2) gave 1.3 g (68%) of the desired product as a white solid.

2-(1-(4-(2-Chlorophenyl)piperazinyl))-N-(2-pyridyl)acetamide (3c). The procedure as described above was used with 1.4 g of 1-(2-chlorophenyl)piperazine, monohydrochloride. Elution with hexane/ethylacetate (7/3) gave 1.4 g (72%) of the desired product as a yellow solid.

2-(1-(4-Pyridylpiperazinyl))-N-(2-pyridyl)acetamide (3d). The procedure as described above was used with 0.9 mL of 1-(2-pyridyl)piperazine. Elution with hexane/ethylacetate (5/5) gave 0.7 g (42%) of the desired product as a yellow solid.

2-(1-(4-Pyrimidylpiperazinyl))-N-(2-pyridyl)acetamide (3e). The procedure as described above was used with 1.2 g of 1-(2-pyrimidyl)piperazine, dihydrochloride. Elution with hexane/ethylacetate (7/3) gave 1.0 g (58%) of the desired product as a brown solid.

General procedure: 1-(Aryl)-4-(2-(2-pyridyl-amino)-ethyl)piperazine (4a-4e): To 5.5 mmol of 2-(1-4-aryl-piperazinyl)-*N*-(2-pyridyl)acetamide dissolved in 30 mL of anhydrous tetrahydrofuran, was added dropwise under N_2 15 mL of lithium aluminum hydride in anhydrous tetrahydrofuran (22 mmol, 4 equiv.). The mixture was heated under reflux (65 °C) for about 2 h, and cooled to room temperature. The resulting mixture was quenched with a solution of saturated ammonium chloride at 0 °C and extracted two times with dichloromethane. The organic layer was washed successively with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated by using a rotary evaporator. The residue was purified by a column chromatography.

1-(2-Methoxyphenyl)-4-(2-(2-pyridylamino)ethyl)piperazine (4a). The procedure as described above was used with 1.8 g of 2-(1-(4-(2-methoxyphenyl)piperazinyl))-*N*-(2-pyridyl)-acetamide. Elution with hexane/ethylacetate (8/2) gave 1.3 g (75%) of the desired product as a needle form.

1-(4-Methoxyphenyl)-4-(2-(2-pyridylamino)ethyl)piperazine

(4b). The procedure as described above was used with 1.8 g of 2-(1-(4-(4-methoxyphenyl)piperazinyl))-*N*-(2-pyridyl)-acetamide. Elution with hexane/ethylacetate (7/3) gave 0.9 g (53%) of the desired product as a yellow solid.

1-(2-Chlorophenyl)-4-(2-(2-pyridylamino)ethyl)piperazine (4c). The procedure as described above was used with 1.8 g of 2-(1-(4-(2-chlorophenyl)piperazinyl))-*N*-(2-pyridyl)acetamide. Elution with hexane/ethylacetate (5/5) gave 0.8 g (48%) of the desired product as an oily form.

1-(2-Pyridyl)-4-(2-(2-pyridylamino)ethyl)piperazine (4d). The procedure as described above was used with 1.6 g of 2-(1-(4-pyridylpiperazinyl))-*N*-(2-pyridyl)acetamide. Elution with hexane/ethylacetate (6/4) gave 0.7 g (45%) of the desired product as an oily form.

1-(2-Pyrimidyl)-4-(2-(2-pyridylamino)ethyl)piperazine (4e). The procedure as described above was used with 1.6 g of 2-(1-(4-pyrimidylpiperazinyl))-*N*-(2-pyridyl)acetamide. Elution with hexane/ethylacetate (7/3) gave 0.8 g (55%) of the desired product as an oily form.

Microwave irradiation method.

2-(Chloroacetyl)amido pyridine (2): Chloroacetyl chloride was directly added dropwise into a 50 mL glass vessel containing a solution of 2-aminopyridine (2.8 g, 30 mmol) in dichloroethane (25 mL). The reaction vessel was capped with a TFM teflon cover and placed in a rotor in a microwave (Milestone, Sorisole, Italy). The mixture was irradiated for 5 min at 80 °C in a 300 W. After irradiating it for 5 min, the same procedure as described above was used to gave 4.9 g (97%) of the desired product as a pink solid; mp 110-115 °C; IR (KBr) 3443, 3226, 1683, 1581, 1330, 1198, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ4.2 (2H, s), 7.1 (1H, d), 7.7 (1H, t), 8.2 (1H, d, J = 8.3 Hz), 8.4 (1H, d, J = 4.9 Hz), 8.95 (1H, bs); ^{13}C NMR ($CDCl_3$) δ43.2, 111.4, 121.0, 139.1, 148.2, 150.7, 164.9; EIMS m/z 170.6 (M^+).

General procedure: 2-(1-4-aryl-piperazinyl)-*N*-(2-pyridyl)acetamide (3a-3e): A solution of arylpiperazines (5.9 mmol) and 2-(chloroacetyl)amidopyridine (1.0 g, 6 mmol) in acetonitrile (30 mL) was added into a 50 mL glass vessel containing the K_2CO_3 (1.6 g, 12 mmol). The reaction vessel was capped with a TFM teflon cover and placed in a rotor in a microwave reactor. The mixture was irradiated for 5 (**3a**, **3b**) or 20 min (**3c-3e**) at 80 °C in a 300 W. After irradiating it for 5-20 min, the reaction mixture was cooled to room temperature. And the same procedure as described above was used for the remainder of the synthesis.

2-(1-(4-(2-Methoxyphenyl)piperazinyl))-N-(2-pyridyl)acetamide (3a). With the exception of the irradiation time, 5 min, the same procedure as described above was used: 1.0 mL of 1-(2-methoxyphenyl)piperazine. Elution with hexane/ethylacetate (8/2) gave 1.5 g (81%) of the desired product as a white solid; mp 84 °C; IR (KBr) 3333, 3302, 1696, 1593, 1301, 1181 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.8 (4H, m), 3.2 (4H, m), 3.8 (3H, s), 6.8-7.1 (5H, m), 7.7 (1H, m), 8.95 (1H, bs); ^{13}C NMR ($CDCl_3$) δ 51.5 54.1 56.1, 65.3, 115.0, 119.0, 120.5, 138.5, 145.2, 148.3, 151.0, 154.5; EIMS m/z 327 $(M+1)^+$, 326 (M^+).

2-(1-(4-(4-Methoxyphenyl)piperazinyl))-N-(2-pyridyl)acetamide (3b). With the exception of the irradiation time of 5 min, the same procedure as described above was used: 1.5 g of 1-(4-methoxyphenyl)piperazine, dihydrochloride. Elution with hexane/ethylacetate (8/2) gave 1.4 g (75%) of the desired product as a white solid; mp 125-130 °C; IR (KBr) 3448, 3301, 1688, 1574, 1299, 1181 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.8 (4H, m), 3.1 (4H, m), 3.2 (2H, s), 3.7 (3H, s), 6.7 (2H, m), 6.8 (2H, m), 6.9 (1H, t), 7.7 (1H, m), 8.2 (1H, dd, J = 5.9 Hz, J' = 8.3 Hz), 9.5 (1H, bs); ^{13}C NMR ($CDCl_3$) δ 51.3, 54.0, 56.0, 65.5, 114.7, 114.9, 119.0, 120.3, 138.7, 145.6, 148.4, 151.4, 154.7; EIMS m/z 326 (M^+).

2-(1-(4-(2-Chlorophenyl)piperazinyl))-N-(2-pyridyl)acetamide (3c). With the exception of the irradiation time of 20 min, the same procedure as described above was used: 1.4 g of 1-(2-chlorophenyl)piperazine, monohydrochloride. Elution with hexane/ethylacetate (7/3) gave 1.7 g (87%) of the desired product as a yellow solid. mp 104-107 °C; IR (KBr) 3447, 3316, 1694, 1588, 1282, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.9 (4H, m), 3.2 (4H, m), 3.2 (2H, s), 6.9-7.1 (3H, m), 7.2 (1H, d, J = 7.5 Hz), 7.4 (1H, d, J = 7.8 Hz), 7.7 (1H, m), 8.3 (2H, dd, J = 5.7 Hz, J' = 16.2 Hz), 9.6 (1H, bs); ^{13}C NMR ($CDCl_3$) δ51.1, 54.0, 62.4, 114.5, 120.4, 121.0, 124.6, 128.1, 129.3, 131.1, 138.9, 148.2, 151.3; EIMS m/z 331.1 $(M+1)^+$, 330 (M^+).

2-(1-(4-Pyridylpiperazinyl))-N-(2-pyridyl)acetamide (3d). With the exception of the irradiation time of 20 min, the same procedure as described above was used: 0.9 mL of 1-(2-pyridyl)piperazine. Elution with hexane/ethylacetate (5/5) gave 1.2 g (72%) of the desired product as a yellow solid; mp 125 °C; IR (KBr) 3435, 3311, 1700, 1297, 1184 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.7 (4H, m), 3.2 (2H, s), 3.6 (4H, m), 6.5 (1H, d), 6.6 (2H, m), 7.5 (1H, m), 7.7 (1H, m), 8.1-8.3 (2H, m), 9.6 (1H, bs); ^{13}C NMR ($CDCl_3$) δ; EIMS m/z 299 $(M+2)^+$, 298 $(M+1)^+$.

2-(1-(4-Pyrimidylpiperazinyl))-N-(2-pyridyl)acetamide (3e). With the exception of the irradiation time of 20 min, the same procedure as described above was used: 1.4 g of 1-(2-pyrimidyl)piperazine, dihydrochloride. Elution with hexane/ethylacetate (7/3) gave 1.1 g (65%) of the desired product as a brown solid; mp 126-128 °C; IR (KBr) 3436, 3303, 1698, 1297, 1189 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.8 (4H, m), 3.2 (4H, m), 3.3 (2H, s), 3.8 (3H, s), 6.5-7.1 (3H, m), 7.6-7.9 (2H, m), 8.3 (2H, m), 9.6 (1H, bs); ^{13}C NMR ($CDCl_3$) δ43.7, 44.2, 110.9, 114.3, 118.8, 139.6, 146.2, 152.8, 154.2, 158.2, 161.9; EIMS m/z 299 $(M+1)^+$, 298 (M^+).

General procedure: 1-(aryl)-4-(2-(2-pyridylamino) ethyl)piperazine (4a-4e): Lithium aluminum hydride (11.0 mmol, 4 equiv.) in anhydrous tetrahydrofuran (7.5 mL) was directly added dropwise into a 50 mL glass vessel containing the solution of 2-(1-4-arylpiperazinyl)-*N*-(2-pyridyl)acetamide (2.75 mmol) in anhydrous tetrahydrofuran (15 mL). The reaction vessel was capped with a TFM teflon cover and placed in a rotor in a microwave reactor. The mixture was irradiated for 5 min at 80 °C in a 300 W. After irradiating for 5 min, the remainder of the synthesis used the same procedure as described above.

1-(2-Methoxyphenyl)-4-(2-(2-pyridylamino)ethyl)piperazine

(4a). The procedure as described above was used with 0.9 g of 2-(1-(4-(2-methoxyphenyl)piperazinyl))-*N*-(2-pyridyl)-acetamide. Elution with hexane/ethylacetate (8/2) gave 1.6 g (92%) of the desired product as a needle form; mp 63-64 °C; IR (KBr) 3407, 3269, 2955, 1359, 1309, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.8 (6H, m), 3.1 (4H, m), 3.4 (2H, s), 3.8 (3H, s), 6.4 (1H, d), 6.5 (1H, t), 6.9-7.1 (4H, m), 7.4 (1H, t), 8.1 (1H, d); ^{13}C NMR ($CDCl_3$) δ 38.7, 50.7, 53.6, 55.8, 57.3, 107.8, 111.7, 113.1, 118.7, 121.4, 123.5, 137.7, 141.5, 148.3, 152.7, 159.1; EIMS m/z 313 $(M+1)^+$.

1-(4-Methoxyphenyl)-4-(2-(2-pyridylamino)ethyl)piperazine (4b). The procedure as described above was used with 0.9 g of 2-(1-(4-(4-methoxyphenyl)piperazinyl))-*N*-(2-pyridyl)-acetamide. Elution with hexane/ethylacetate (7/3) gave 1.3 g (80%) of the desired product as a yellow solid; mp 82-85 °C; IR (KBr) 3405, 3248, 2948, 1358, 1270, 1186 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.9 (6H, m), 3.2 (4H, m), 3.6 (2H, s), 3.8 (3H, s), 5.7 (1H, bs), 6.5 (2H, m), 6.9 (4H, m), 7.4 (1H, m), 8.1 (1H, d, J = 3.8 Hz); ^{13}C NMR ($CDCl_3$) δ 38.3, 50.2, 53.7, 55.5, 57.1, 107.5, 112.1, 113.3, 118.5, 121.1, 123.1, 137.2, 141.1, 148.5, 152.7, 158.8; EIMS m/z 313 $(M+1)^+$.

1-(2-Chlorophenyl)-4-(2-(2-pyridylamino)ethyl)piperazine (4c). The procedure as described above was used with 0.9 g of 2-(1-(4-(2-chlorophenyl)piperazinyl))-*N*-(2-pyridyl)acetamide. Elution with hexane/ethylacetate (5/5) gave 1.3 g (78%) of the desired product as an oily form; IR (neat) 3447, 3316, 2942, 1375, 1303, 1286, 1201 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.9 (6H, m), 3.2 (4H, m), 3.3 (2H, m), 5.1 (1H, bs), 6.3 (1H, d, J = 8.4 Hz), 6.5 (1H, m), 6.9 (3H, m), 7.2-7.3 (2H, m), 8.0 (1H, d, J = 3.9 Hz); ^{13}C NMR ($CDCl_3$) δ 38.9, 51.7, 53.4, 57.1, 107.4, 113.1, 120.8, 124.1, 128.0, 129.2, 131.0, 137.7, 148.6, 149.7, 159.2; EIMS m/z 317 (M^+).

1-(2-Pyridyl)-4-(2-(2-pyridylamino)ethyl)piperazine (4d). The procedure as described above was used with 0.8 g of 2-(1-(4-pyridylpiperazinyl))-*N*-(2-pyridyl)acetamide. Elution with hexane/ethylacetate (6/4) gave 1.0 g (65%) of the desired product as an oily form; IR (neat) 3373, 2995, 2924, 1379, 1309, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.6 (6H, m), 3.3 (2H, m), 3.5 (4H, m), 5.1 (1H, bs), 6.3-6.6 (4H, m), 7.4 (2H, m), 8.0 (1H, t), 8.1 (1H, d, J = 4.1 Hz); ^{13}C NMR ($CDCl_3$) δ 38.9, 51.7, 53.4, 57.1, 107.4, 113.1, 120.8, 124.1, 128.0, 129.2, 131.0, 137.7, 148.6, 149.7, 159.2; EIMS m/z 284 $(M+1)^+$.

1-(2-Pyrimidyl)-4-(2-(2-pyridylamino)ethyl)piperazine (4e). The procedure as described above was used with 0.8 g of 2-(1-(4-pyrimidylpiperazinyl))-*N*-(2-pyridyl)acetamide. Elution with hexane/ethylacetate (7/3) gave 0.9 g (63%) of the desired product as an oily form; IR (neat) 3436, 3303, 2927, 1360, 1305, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.8 (6H, m), 3.1 (4H, m), 3.4 (2H, s), 3.8 (3H, s), 6.4 (1H, d), 6.5 (1H, t), 6.8-7.1 (4H, m), 7.4 (1H, t), 8.1 (1H, d); ^{13}C NMR ($CDCl_3$) δ 38.8, 53.2, 57.4, 60.8, 107.9, 110.4, 113.2, 137.9, 148.0, 158.1, 158.9, 168.1; EIMS m/z 285 $(M+1)^+$.

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References

1. Wilma, K.; Ineke, W.; Chris, G. K.; Marian, H. A.; Martin, T. M. T.; Adriaan, P. I. *J. Med. Chem.* **1995**, *38*, 1942-1954.
2. (a) Yong, S.; Frederick, J. M.; Mark, A. M.; Pedro, A. J.; Mark, W. H.; David, R. S. *J. Biol. Chem.* **1993**, *24*, 18200-18204. (b) Jose, J. L.; Rene, H. *Trends Pharmacol. Sci.* **1995**, *16*, 246-252. (c) Daniel, H.; Graeme, R. M. *Behav. Brain Res.* **1996**, *73*, 263-268. (d) Daniel, H.; Jason, P. H.; Graeme, R. M. *Phmacolo. Biochem. Be.* **2002**, *71*, 533-554.
3. (a) Sven, E. H.; Lena, B.; Yi, L. L.; Bjoern, S.; Svante, R.; Nils, E. A.; Uli, H. *J. Med. Chem.* **1990**, *33*, 1541-1544. (b) Revathi, K. R.; Laura, R. F.; Milt, T.; Richard, A. G. *J. Med. Chem.* **1991**, *34*, 2633-2638. (c) Zhi-Ping, Z.; Mei-Ping, K.; Hank, F. K. *J. Med. Chem.* **1994**, *37*, 1406-1407.
4. (a) Pramod, R. S. *Pharmac. Ther.* **1995**, *66*, 339-368.
5. Julien, S.; Timothy, N. D.; Gabriele, W. *Tetrahedron Lett.* **2004**, *45*, 7675-7677.
6. (a) Laurence, P.; Andre, L. *Tetrahedron* **2001**, *57*, 9199-9223. (b) Edward, J. H.; William, J. K.; Euan, J. M. *Chem. Commun.* **2002**, 2262-2263. (c) Olivier, C.; Karine, G.; Jack, H.; Ludovic, P.; Francoise, T. B.; Loic, T. *Tetrahedron Lett.* **2004**, *45*, 391-395. (d) Bernd, H. *Tetrahedron Lett.* **2004**, *45*, 2219-2221.
7. (a) Francois, R. A.; Amaya, B.; Roger, W.; Thierry, B. *Tetrahedron Lett.* **2003**, *44*, 4455-4458. (b) Jayadevan, J.; Rathna, D. M.; Raghavachary, R. *Tetrahedron Lett.* **2004**, *45*, 7303-7305. (b) Abramovitch, *R. A. Org. Prep. Proced. Int.* **1991**, *23*, 685-712. (c) Yadav, J. S.; Reddy, B. V. S.; Madan, C.; Kumar, G. M. *Synlett* **2001**, 1781-1783.