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Practical Application of the Palladium-catalyzed Amination in Phenylpiperazine Synthesis: An Efficient Synthesis of a Metabolite of the Antipsychotic Agent Aripiprazole

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Abstract: A metabolite of Aripiprazole (**1**), 7-[4-[4-(2,3-dichloro-4-hydroxyphenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (**2**), was prepared by the coupling reaction of 1-(4-benzyloxy-2,3-dichlorophenyl)-piperazine (**11**) with 7-(4-chlorobutoxy)-3,4-dihydro-2(1*H*)-quinolinone (**16**). The palladium-catalyzed amination of contiguous tri- and tetra-substituted benzenes with piperazine derivatives was investigated. The key intermediate **11** was efficiently prepared using the palladium-catalyzed amination of phenyl bromide **15** with piperazine.

The 2(1*H*)-quinolinone derivative, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (Aripiprazole, **1**), a novel antipsychotic agent, was synthesized by Oshiro and co-workers.[1] It possesses both the post dopamine (DA) receptor antagonist (D_2-antagonist) and DA autoreceptor agonist activity. In recent studies on the metabolism of **1**, one metabolite **2** was isolated from the biological fluids of rat, whose nuclear magnetic resonance (NMR) and mass (MS) spectral data[2] indicated the structure of a 4-hydroxy-phenylpiperazine compound (Figure 1). We have been interested in the synthesis of **2**, especially the highly substituted core, a 1-(2,3-dichloro-4-hydroxyphenyl)piperazine moiety. We initiated the synthesis of **2** in order to confirm the structure of the main metabolite, to compare its pharmacological activity and to establish the effective synthesis of **2**.

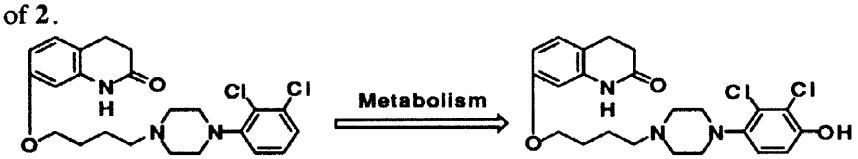

Figure 1

In general, substituted phenylpiperazines have been prepared by the reaction of various aniline derivatives with bis(2-halogenoethyl)amine hydrohalides[3a,b] or by the nucleophilic substitution of phenyl halides having electron-withdrawing groups with piperazines. There are some drawbacks to these methods. In the former case, the ortho and para isomers are often contaminants when preparing the nitro compounds which are the precursors of the aniline derivatives. The purification of the resulting piperazine derivative is complicated because of poor yield, and bis(2-bromoethyl)amine hydrobromide is very poisonous. In the latter case, it is difficult to introduce

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a piperazine part into the desired position of the benzene ring.

Recently, Buchwald *et al.* and Hartwig *et al.* have independently reported the palladium-catalyzed amination of aryl bromides,[4a-i] iodides[4j,k] and triflates[4l-o] with primary or secondary amines and anilines. This new amination has a broad substrate scope in which electron-rich or electron-poor phenyl halides can be combined with primary and secondary amines to afford the desired aryl amine products in moderate to excellent yields. After we attempted the synthesis of phenylpiperazine **11** using the usual procedure, we tried to improve the synthetic efficiency using the palladium-catalyzed amination (Figure 2). We now here describe the efficient preparation of **2**.

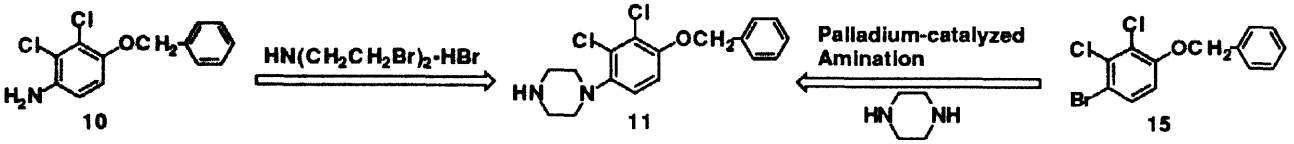
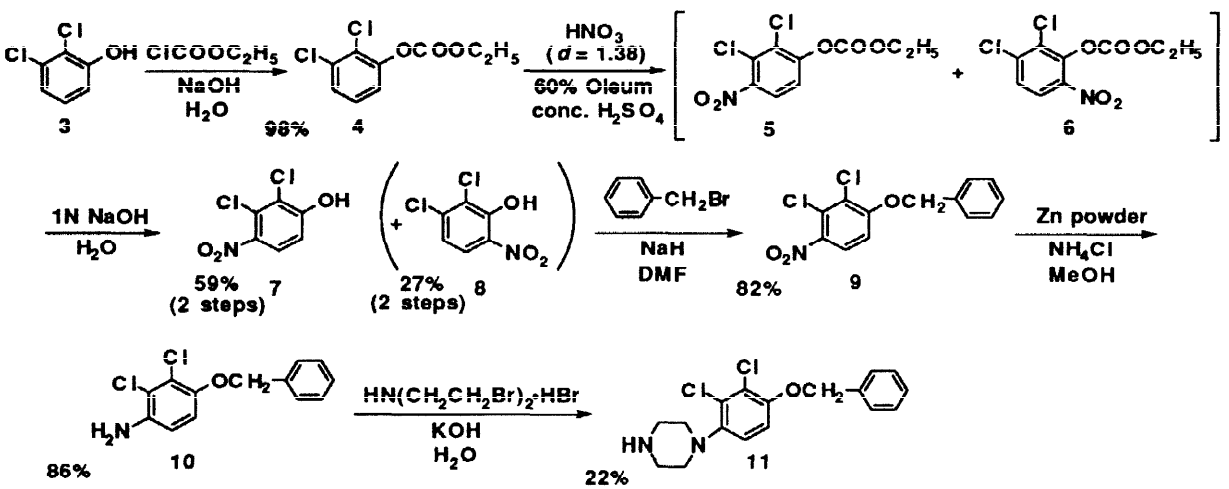


Figure 2

(1) Classical Phenylpiperazine Synthesis.

We first constructed the key intermediate **11** using the usual synthetic procedures as illustrated in Scheme 1. Compound **4** was prepared by the reaction of 2,3-dichlorophenol (**3**) with ethyl chloroformate in the presence of sodium hydroxide (NaOH) in water in 98% yield. Nitration of the carbonate **4** with nitric acid (HNO_3, d = 1.38) in fuming sulfuric acid (free SO_3 content 60%, 60% oleum) and concentrated sulfuric acid (H_2SO_4), followed by treatment of the mixture of **5** and **6** with 1 N NaOH in water, gave the 4-nitrophenol compound **7**[5] and 6-nitrophenol compound **8**[6a,b] in 59% and 27% yield after purification by silica gel column chromatography, respectively. Benzylation of the 4-nitrophenol **7** with benzyl bromide in the presence of sodium hydride (NaH) in *N*,*N*-dimethylformamide (DMF) afforded the benzyloxyphenyl derivative **9** in 82% yield, which was hydrogenated with zinc (Zn) in the presence of ammonium chloride (NH_4Cl) in methanol (MeOH) to give the aniline derivative **10** in 86% yield. The desired intermediate phenylpiperazine **11** was prepared by condensation of the aniline **10** with bis(2-bromoethyl)amine hydrobromide in the presence of potassium hydroxide (KOH) in water in 22% yield. The key intermediate **11** was prepared from 2,3-dichlorophenol (**3**) in 9% overall yield in 6 steps. The ring closure reaction had a poor yield and the synthetic process was troublesome.

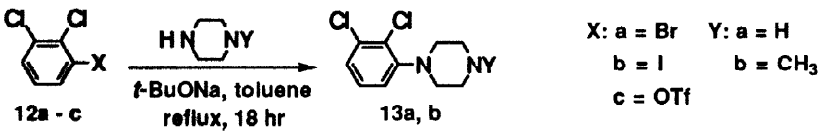


Scheme 1

(2) Phenylpiperazine Synthesis by the Palladium-catalyzed Amination.

Recent papers[4a-n] concerning the palladium-catalyzed amination of phenyl halides including triflates prompted us to apply this methodology for the development of an effective procedure for the synthesis of phenylpiperazines. As an application for the synthesis of medical drugs, we investigated the synthesis of contiguous tri-substituted phenylpiperazines using the palladium-catalyzed amination. In preliminary studies, we attempted the palladium-catalyzed amination of 1,2,3-trihalogeno-substituted benzenes, 1-halogeno-2,3-dichlorobenzene or 2,3-dichlorophenyl trifluoromethanesulfonate, with piperazine or *N*-methylpiperazine as summarized in Table 1.

Table 1 Palladium-catalyzed Aromatic Amination



Entry	X	Y	Reaction conditions	Yield (%)*
1	Br	H	3 mol% $PdCl_2[P(o\text{-tol})_3]_2$	0
2	Br	CH_3	2 mol% $Pd_2(dba)_3$, 6 mol% (*R*)-BINAP	58
3	I	CH_3	2 mol% $Pd_2(dba)_3$, 6 mol% (*R*)-BINAP	59
4	Br	H	0.2 mol% $Pd_2(dba)_3$, 0.6 mol% (*R*)-BINAP	26
5	Br	H	1 mol% $Pd_2(dba)_3$, 3 mol% (*R*)-BINAP	58
6	Br	H	2 mol% $Pd_2(dba)_3$, 6 mol% (*R*)-BINAP	62**
7	I	H	2 mol% $Pd_2(dba)_3$, 6 mol% (*R*)-BINAP	66
8	OTf	CH_3	2 mol% $Pd_2(dba)_3$, 6 mol% (*R*)-BINAP	trace
9	OTf	CH_3	4 mol% $Pd(OAc)_2$, 8 mol% (*R*)-BINAP	8

* Isolated yield.

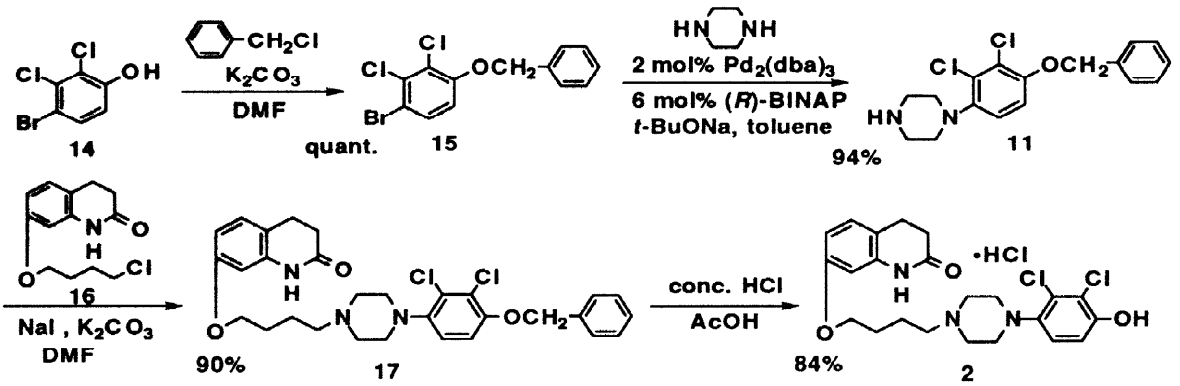
** 1,1'-(2-Chloro-1,3-phenylene)bispiperazine (**13c**) as a byproduct was obtained in 7% yield.

As far as we know, there is no palladium-catalyzed amination of 1,2,3-trihalogeno-substituted benzenes with piperazine derivatives. The palladium-catalyzed amination of contiguous halogeno-substituted benzene is the only reaction of 1-bromo-2-iodobenzene with morpholine.[4j] We considered it difficult that the amination would proceed with a good yield because of the electron deficiency of the benzene ring of phenyl halides, and furthermore, the bulkiness of the benzene derivatives. Therefore, a slightly large amount of $Pd_2(dba)_3$ and (*R*)-BINAP were used. Although Buchwald's group[4c] had reported that both racemic and nonracemic BINAP gave similar results in the amination reaction, we employed the optically active compound which was readily available and inexpensive. As shown in Table 1, the amination of the 1-halogeno-2,3-dichlorobenzenes with piperazine or *N*-methylpiperazine proceeded with moderate yields using the $Pd_2(dba)_3$/(*R*)-BINAP catalyst system (entries 2, 3 and 5 - 7). The use of $Pd_2(dba)_3$ at low catalyst loading (0.2 mol% Pd) gave a low yield (entry 4). The yield of the coupled product was improved to 62% yield with a relatively high catalyst loading (2 mol% Pd) (entry 6).

On the other hand, the reaction of phenyl triflate with *N*-methylpiperazine hardly occurred by contraries (entries 8 and 9). We thus established an effective preparation of 1-(2,3-dichlorophenyl)piperazine (**13a**)[3a,b] which was an essential component for the synthesis of the mother compound **1**, and considered that the synthesis of **13a** using the palladium-catalyzed amination of commercially available and cheap 2,3-dichlorobromobenzene[7] with piperazine was significant in view of our medicinal needs.

(3) Synthesis of the Metabolite 2.

We next planned to establish the preparation of the key intermediate **11** by the palladium-catalyzed amination of the highly substituted phenyl bromide with piperazine according to the method already mentioned, as shown in Scheme 2. We employed 4-bromo-2,3-dichlorophenol (**14**)[8] as the starting material, which was converted in a quantitative yield to 1-benzyloxy-4-bromo-2,3-dichlorobenzene (**15**) by the treatment of benzyl chloride with potassium carbonate (K_2CO_3) in DMF. The palladium-catalyzed amination of a contiguous tetra-substituted benzene **15** with piperazine gave the desired phenylpiperazine **11** in 94% yield. It was suggested that the amination regioselectively proceeded with a excellent yield as compared with the results described in Table 1 because the existence of a bulky benzyloxy group on the benzene ring disturbed the reaction of the neighboring chloride with piperazine. Coupling reaction of the phenylpiperazine **11** with the chloride **16**[1] carried out in the presence of K_2CO_3 and sodium iodide (NaI) in DMF to give the coupling product **17** in 90% yield. Deprotection of the benzyl group from the coupling product **17** with concentrated hydrochloric acid (HCl) in acetic acid (AcOH) afforded the desired compound **2** in 84% yield. The target compound **2** was prepared from 4-bromo-2,3-dichlorophenol (**14**) in 71% overall yield in 4 steps. The structure of the metabolite **2** was identical with that of the corresponding synthetic compound **2** on the basis of nuclear magnetic resonance (NMR), mass spectrum (MS) and high performance liquid chromatographic (HPLC) comparisons.[2] The activities of the dopamine receptor antagonist of **2** were found to give similar results.[1]



Scheme 2

In conclusion, we have investigated the palladium-catalyzed amination of contiguous tri- and tetra-substituted benzenes with piperazine derivatives and established an efficient synthesis of the key intermediate **11**. The key intermediate **11** was converted to **2** by a coupling reaction with the chloride **16** followed by deprotection of the benzyl group. The structure of the metabolite **2**[2] was identical with the synthetic compound **2** based on spectral comparisons.

Experimental Section

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer Spectrum 1000. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE DPX 250 spectrometer. Mass spectra (MS) were obtained on Finnigan MAT GCQ instruments. Silica gel (Fuji silysia chemical Ltd., BW-127ZH) was used for column chromatography. Preparative thin layer chromatography (PLC) was carried out on plates (20 x 20 cm, 0.5 mm, thickness) precoated with silica gel ($60F_{254}$, Merck Art 5744).

Ethyl 2,3-dichlorophenyl carbonate (4). Ethyl chloroformate (3.26 g, 30 mmol) was added dropwise to a mixture of **3** (4.89 g, 30 mmol) and NaOH (1.20 g, 30 mmol) in water (30 ml) at room temperature. After the mixture was stirred at room temperature for 1.5 h, the mixture was poured into 10% aqueous NaOH and extracted with Et_2O. The extracts were dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The residue was recrystallized from hexane to give **4** (6.91 g, 98%) as colorless needles, mp 51 ℃. ^{1}H-NMR ($CDCl_3$) δ : 1.41 (3H, t, J = 7.1 Hz), 4.36 (2H, q, J = 7.1 Hz), 7.10 - 7.30 (2H, m), 7.39 (1H, dd, J = 7.1, 2.0 Hz). IR (KBr) : 2982, 1765, 1456, 1373, 1277, 1239, 1000, 868 cm^{-1}. MS *m/z* (%) : 263 (29, M^+), 208 (13), 190 (12), 164 (62), 162 (100), 133 (10), 126 (23), 73 (26). *Anal.* Calcd for $C_9H_8Cl_2O_3$: C, 45.99; H, 3.43. Found : C, 45.87; H, 3.45.

Nitration of 4. 2,3-Dichloro-4-nitrophenol (7)[5] and 2,3-dichloro-6-nitrophenol (8)[6a,b]. Nitric acid (d = 1.38, 12 ml, 160 mmol) was added dropwise to a mixture of concentrated H_2SO_4 (30 ml) and 60 % oleum (30 ml) at 4 ℃ and then **4** (18.81 g, 80 mmol) was added to the reaction mixture at 5 - 10 ℃. After the mixture was stirred at 5 ℃ for 2 h, it was poured into ice-water and extracted with Et_2O. The extracts were dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The residue was added to a mixture of 5 N NaOH (40 ml) and water (50 ml), and the mixture was stirred at 80 ℃ for 0.5 h. The mixture was cooled to about 4 ℃, which was acidified by addition of concentrated HCl (15 ml) and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2) to give **7** (9.84 g, 59%) as a pale brown powder and **8** (4,50 g, 27%) as a yellow powder. **7**; ^{1}H-NMR ($CDCl_3$) δ : 6.23 (1H, broad s), 7.07 (1H, d, J = 9.5 Hz), 7.89 (1H, d, J = 9.5 Hz). **8**; ^{1}H-NMR ($CDCl_3$) δ : 7.15 (1H, d, J = 9.2 Hz), 8.03 (1H, d, J = 9.2 Hz), 11.28 (1H, broad s).

2,3-Dichloro-4-benzyloxynitrobenzene (9). To a solution of **7** (9.36 g, 45 mmol) in DMF (95 ml) was added 60 % NaH (2.16 g, 54 mmol) at 4 ℃. After the mixture was stirred at 4 ℃ for 20 min, benzyl bromide (8.62 g 50.4 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight. The mixture was poured into ice-water and extracted with AcOEt - toluene (5 : 1). The extracts were dried over Na_2SO_4 and evaporated off. The residue was purified by column chromatography (silica gel; eluent, AcOEt : hexane = 1 : 8) to give **9** (11.04 g, 82%) as a pale yellow powder. An analytical sample of **9** was recrystallized from AcOEt - hexane as pale yellow needles, mp 88 - 89 ℃. ^{1}H-NMR ($CDCl_3$) δ : 5.27 (2H, s), 6.96 (1H, d, J = 9.2 Hz), 7.30 - 7.55 (5H, m), 7.85 (1H, d, J = 9.2 Hz). IR (KBr) : 1568, 1524, 1454, 1339, 1280, 995, 816, 757 cm^{-1}. MS *m/z* (%) : 299 (17), 297 (100, M^+), 182 (34), 269 (13), 267 (17), 178 (28), 176 (43), 91 (100). *Anal.* Calcd for $C_{13}H_9Cl_2NO_3$: C, 52.38; H, 3.04; N, 4.70. Found : C, 52.53; H, 2.86; N, 4.51.

2,3-Dichloro-4-benzyloxyaniline (10). To a solution of **9** (10.55 g, 36 mmol) in MeOH (200 ml) was

added NH_4Cl (9.63 g, 180 mmol) and Zn powder (47.07 g, 720 mmol) at 70 ℃. After the mixture was gently refluxed for 1 hr, the insoluble materials were removed by filtration and washed with MeOH. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, AcOEt : hexane = 1 : 4) to give **10** (9.01 g, 86%) as a pale yellow powder. An analytical sample of **10** was recrystallized from Et_2O - hexane as pale yellow needles, mp 56 - 57 ℃. ^{1}H-NMR ($CDCl_3$) δ : 3.91 (2H, broad s), 5.06 (2H, s), 6.61 (1H, d, J = 8.9 Hz), 6.77 (1H, d, J = 8.9 Hz), 7.25 - 7.55 (5H, m). IR (KBr) : 3394, 3293, 1600, 1486, 1454, 1277, 1036, 803, 695 cm^{-1}. MS *m/z* (%) : 269 (26), 267 (43, M^+), 178 (23), 176 (34), 91 (100), 65 (24). *Anal.* Calcd for $C_{13}H_{11}Cl_2NO$: C, 58.23; H, 4.13; N, 5.22. Found : C, 58.04; H, 3.69; N, 4.92.

1-(4-Benzyloxy-2,3-dichlorophenyl)piperazine (11). To a mixture of **10** (3.47 g, 18 mmol) and bis(2-bromoethyl)amine hydrobromide (4.37 g, 14 mmol) in water (2 ml) was added KOH (85 %, 0.53 g, 8 mmol) in water (1 ml) at 90 ℃ in three portions during 90 min. The mixture was stirred at 90 ℃ for 3 h. The mixture was poured into 10 % aqueous NaOH (7 ml) and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 40 : 1 → 20 : 1) to give **11** (1.04 g, 22%) as a pale yellow powder. An analytical sample of **11** was transformed into its hydrochloride salt by the addition of 10 % HCl - MeOH (25 ml) followed by the concentration to dryness *in vacuo*. The residue was recrystallized from EtOH as colorless needles, mp 252 - 255 ℃ (dec.). ^{1}H-NMR (DMSO-d_6) δ : 3.05 - 3.15 (4H, m), 3.15 - 3.25 (4H, m), 5.21 (2H, s), 7.16 (1H, d, J = 9.0 Hz), 7.21 (1H, d, J = 9.0 Hz), 7.25 - 7.50 (5H, m), 9.05 (2H, broad). IR (KBr) : 2930, 2713, 2474, 1590, 1477, 1450, 1294, 1047, 806, 748 cm^{-1}. MS *m/z* (%) : 336 (40, M^+), 249 (10), 247 (65), 245 (100), 209 (10), 91 (15), 83 (11). *Anal.* Calcd for $C_{17}H_{18}Cl_2NO_2$•HCl : C, 54.64; H, 5.12; N, 7.50. Found : C, 54.71; H, 5.26; N, 7.47.

General procedure for aromatic amination reactions using palladium catalyst.

1-(2,3-Dichlorophenyl)-4-methylpiperazine (13b). A mixture of 3-bromo-1,2-dichlorobenzene (**12a**) (113 mg, 0.5 mmol), *N*-methylpiperazine (65 mg, 0.65 mmol), *t*-BuONa (67 mg, 0.7 mmol), (*R*)-BINAP (9.3 mg, 0.015 mmol) and $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) in dry toluene (6 ml) was gently refluxed with stirring under a nitrogen atmosphere for 18 h. The mixture was filtrated by a pad of Celite and the filtrate was extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and evaporated off. The residue was purified by thin layer chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 10 : 1) to give **13b** (71 mg, 58%) as a pale yellow oil. An analytical sample was **13b** was transformed into its hydrochloride salt by the addition of 10 % HCl - MeOH (5 ml) followed by the concentration to dryness *in vacuo*. The residue was recrystallized from EtOH - *n*-hexane as pale yellow needles, mp 249 - 250 ℃. ^{1}H-NMR (DMSO-d_6) δ : 2.81 (3H, s), 3.00 -3.70 (8H, m), 7.15 - 7.25 (1H, m), 7.25 - 7.40 (2H, m), 11.01 (1H, broad). IR (KBr) : 3438, 2553, 2442, 1579, 1455, 1424, 1248, 1053, 958, 780, 714 cm^{-1}. MS *m/z* (%) : 245 (65, M^+), 244 (100), 229 (18), 209 (51), 202 (20), 187 (14), 173 (34), 166 (32), 85 (20), 66 (17). *Anal.* Calcd for $C_{11}H_{14}Cl_2N_2$•HCl : C, 46.92; H, 5.37; N, 9.95. Found : C, 46.86; H, 5.21; N, 9.99.

1-(2,3-Dichlorophenyl)piperazine (13a)[3a,b]. **13a** (72 mg, 62% as a yellow oil) and **1,1'-(2-chloro-1,3-phenylene)bispiperazine (13c)** (10 mg, 7% as a pale yellow oil) as a byproduct were prepared by a general procedure described previously with **12a** (113 mg, 0.5 mmol), piperazine (258 mg, 3 mmol), (*R*)-BINAP (9.3 mg, 0.015 mmol), *t*-BuONa (67 mg, 0.7 mmol) and $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) in dry

toluene (6 ml). **13a;** ^{1}H-NMR ($CDCl_3$) δ : 2.95 - 3.20 (8H, m), 6.90 - 7.00 (1H, m), 7.10 - 7.20 (2H, m). **13c;** ^{1}H-NMR ($CDCl_3$) δ : 2.95 - 3.15 (16H, m), 6.79 (1H, d, J = 8.0 Hz), 7.18 (2H, d, J = 8.0 Hz). IR (neat) : 2944, 2823, 1577, 1471, 1456, 1244, 1137, 995, 790, 754 cm^{-1}. MS *m/z* (%) : 280 (38, M^+), 238 (100), 229 (11), 202 (18), 187 (33), 173 (15), 159 (11), 147 (12), 75 (28).

3-Benzyloxy-4-bromo-1,2-dichlorobenzene (15). A mixture of **14** (7.26 g, 30 mmol), benzyl chloride (4.94 g, 39 mmol), K_2CO_3 (5.39 g, 39 mmol) in DMF (65 ml) was stirred at room temperature overnight. The mixture was poured into ice-water and extracted with AcOEt - toluene (5 : 1). The extracts were dried over Na_2SO_4 and evaporated off. The residue was purified by column chromatography (silica gel; eluent, AcOEt : hexane = 1 : 15) to give **15** (9.97 g, quantitative yield) as a white powder. An analytical sample of **15** was recrystallized from AcOEt - hexane as colorless needles, mp 89 - 91 ℃. ^{1}H-NMR ($CDCl_3$) δ : 5.16 (2H, s), 6.78 (1H, d, J = 8.9 Hz), 7.25 - 7.50 (6H, m). IR (KBr) : 1574, 1448, 1384, 1280, 1258, 1075, 1019, 802, 746, 697 cm^{-1}. MS *m/z* (%) : 197 (100, M^+), 182 (34), 180 (46), 179 (74), 164 (47), 154 (47), 153 (58), 127 (97), 126 (42), 125 (45). *Anal.* Calcd for $C_{13}H_9Cl_2BrO$: C, 47.03; H, 2.73. Found : C, 47.15; H, 2.74.

1-(4-Benzyloxy-2,3-dichlorophenyl)piperazine (11) by the palladium-catalyzed amination. Compound **11** (2.52 g, 94% as a pale yellow powder) was prepared by a general procedure described previously with **15** (2.66 g, 8 mmol), piperazine (4.13 g, 48 mmol), *t*-BuONa (1.08 g, 11.2 mmol), (*R*)-BINAP (149 mg, 0.24 mmol) and $Pd_2(dba)_3$ (61 mg, 0.064 mmol) in dry toluene (80 ml). An analytical sample of **11** was transformed into its hydrochloride salt by the addition of 10 % HCl - MeOH (8 ml) followed by the concentration to dryness *in vacuo*. The residue was recrystallized from EtOH as colorless needles, mp 252 - 255 ℃ (dec.). ^{1}H-NMR (DMSO-d_6) δ : 3.05 - 3.15 (4H, m), 3.15 - 3.25 (4H, m), 5.21 (1H, s), 7.16 (1H, d, J = 9.0 Hz), 7.21 (1H, d, J = 9.0 Hz), 7.25 - 7.50 (5H, m), 9.05 (2H, broad).

7-[4-[4-(4-Benzyloxy-2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (17). A mixture of **11** (0.71 g, 2.1 mmol), **16** (0.51 g, 2 mmol), K_2CO_3 (0.28 g, 2 mmol) and NaI (0.45 g, 3 mmol) in DMF (5 ml) was stirred at 100 ℃ for 2 h. The mixture was concentrated *in vacuo* and ice-water (about 50 ml) was added. The precipitated crystals were collected by filtration and purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 30 : 1) to give **17** (1.00 g, 90%) as a white powder. An analytical sample was recrystallized from EtOH as colorless needles, mp 143 - 144 ℃. ^{1}H-NMR ($CDCl_3$) δ : 1.60 - 1.95 (4H, m), 2.49 (2H, t, J = 6.9 Hz), 2.50 -2.80 (4H, m), 2.89 (2H, t, J = 6.9 Hz), 2.90 - 3.20 (4H, m), 3.96 (2H, t, J = 5.9 Hz), 5.12 (2H, s), 6.36 (1H, dd, J = 8.4, 2.4 Hz), 6.51 (1H, dd, J = 8.4, 2.4 Hz), 6.80 - 7.00 (2H, m), 7.03 (1H, d, J = 8.4 Hz), 7.25 - 7.50 (5H, m), 8.67 (1H, broad s). IR (KBr) : 2942, 2809, 1682, 1627, 1594, 1473, 1450, 1378, 1274, 1177, 1051, 1028, 968, 734 cm^{-1}. MS *m/z* (%) : 553 (19, M^+), 351 (19), 349 (36), 303 (63), 301 (98), 176 (23), 163 (23), 139 (30), 98 (26), 91 (100), 84 (69), 70 (35). *Anal.* Calcd for $C_{30}H_{33}Cl_2N_3O_3$: C, 64.98; H, 6.00; N, 7.58. Found : C, 65.01; H, 6.00; N, 7.48.

7-[4-[4-(2,3-Dichloro-4-hydroxyphenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone hydrochloride (2). A solution of **17** (0.55 g, 1 mmol) in concentrated HCl (6 ml) and AcOH (6 ml) was gently refluxed for 3 h and the mixture was evaporated *in vacuo* . The residue was recrystallized from EtOH to give **2** (0.42 g, 84%) as a white powder, mp 153 - 155 ℃. ^{1}H-NMR ((DMSO-d_6) δ : 1.50 - 2.00 (4H, m), 2.40 (2H, t, J = 7.5 Hz), 2.77 (2H, t, J = 7.5 Hz), 2.95 - 3.50 (10H, m), 3.92 (2H, t, J = 5.7 Hz), 6.44 (1H, d, J = 2.4 Hz), 6.49 (1H, dd, J = 8.2, 2.4 Hz), 6.96 (1H, d, J = 8.9 Hz), 7.04 (1H, d, J = 8.2 Hz), 7.06 (1H,

d, J = 8.9 Hz), 10.00 (1H, s), 10.44 (1H, s), 10.60 (1H, broad). IR (KBr) : 3080, 2602, 1681, 1651, 1626, 1594, 1515, 1495, 1416, 1359, 1297, 1190, 966, 908, 820 cm^{-1}. MS *m/z* (%) : 465 (40), 464 (19), 463 (45, M^+), 429 (19), 428 (17), 427 (40), 303 (13), 261 (65), 259 (100), 163 (13), 98 (22), 84 (50), 70 (60). *Anal.* Calcd for $C_{23}H_{27}Cl_2N_3O_3$•HCl : C, 55.16; H, 5.63; N, 8.39. Found : C, 55.18; H, 5.69; N, 8.32. An identical sample of **2** was transformed into the hydrochloride salt free **2** by the addition of saturated aqueous $NaHCO_3$ (10 ml) and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The residue was recrystallized from DMF-H_2O as a white powder, mp 225 - 226 ℃ (dec). ^{1}H-NMR ((DMSO-d_6) δ : 1.50 - 1.85 (4H, m), 2.25 - 2.65 (8H, m), 2.70 - 2.95 (6H, m), 3.91 (2H, t, J = 6.1 Hz), 6.35 - 6.55 (2H, m), 6.70 - 7.10 (3H, m), 9.98 (1H, s), 10.23 (1H, s).

References and Notes

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2. ^{1}H-NMR ((DMSO-d_6) δ : 1.50 - 1.85 (4H, m), 2.25 - 2.65 (8H, m), 2.70 - 2.95 (6H, m), 3.91 (2H, t, J = 6.1 Hz), 6.35 - 6.55 (2H, m), 6.70 - 7.10 (3H, m), 9.98 (1H, s). MS *m/z* (%) : 465 (40), 464 (20), 463 (55, M^+), 429 (20), 428 (17), 427 (22), 301 (21), 261 (64), 259 (100), 163 (13), 98 (22), 84 (67), 70 (76). HPLC analysis using TSK gel (ODS-80TM, TOSOH, i. d. 4.6 mm x 150 mm), (flow rate, 1.0 ml/min; eluent, CH_3CN : 20 mM aqueous Na_2SO_4 : AcOH = 30 : 70 : 1, detection UV 254 nm). The chromatogram showed the retention time was 10.0 min.
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