# Amino(hetero)arylmethylation of Phenols with *N*-[α-Amino(hetero)arylmethyl]benzotriazoles

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*N*-[α-Amino(hetero)arylmethyl]benzotriazoles derived from a variety of (hetero)aromatic aldehydes were reacted with sodium phenolates to afford amino(hetero)arylmethylated phenols in high yields.

## Introduction

Benzotriazole methodology,[1] using reagents of the type $RCH(NR^1{}_2)Bt$ (Bt = 1-benzotriazolyl), has allowed extensions of Mannich aminomethylation to the general α-aminoalkylation of ketones,[2a,b] esters[3] and aliphatic nitro compounds.[4] The present paper describes our attempts to similarly extend the well-known Mannich aminomethylations of phenols to the analogous α-aminoalkylations. Such an extension is of interest because of the potential utility of phenolic Mannich-type bases as pharmaceuticals,[5a,b] insect growth regulators and sterilants,[6a−c] and photo- and thermochromic substances.[7]

Previous α-aminoalkylations of phenols in the *ortho* position have been reported. Electron-rich naphthols condense with benzaldehydes and secondary amines.[8−11] Recently improved syntheses of such naphthol derivatives have been reported,[12] using preformed immonium salts derived from unsubstituted benzaldehyde. The use of the highly electron-rich 1,3-benzodioxol-5-ol provides Mannich-type products in good yields.[6c,13] However, in contrast to naphthols or alkoxy-substituted phenols, the reported yields for aminoalkylations of methyl and *tert*-butyl phenols[10] are only 13−38%. Electron-deficient methyl 4-hydroxybenzoate afforded a corresponding Mannich-type product in 26% yield,[12] and the condensation of 4-hydroxyacetophenone with methylene-bis-piperidine[14] proceeded in unspecified yields. Usually aromatic aldehydes with electron-donating substituents have been used,[6c,7,13] and less frequently, halogen-substituted benzaldehydes[11] are used.

We now report that the displacement of the benzotriazole moiety from *N*-[α-(dialkylamino)alkyl]benzotriazoles with phenolate anions (Scheme 1) provides a convenient synthesis of phenolic Mannich bases derived from a variety of aromatic and heteroaromatic aldehydes.

## Results and Discussion

**Preparation of the Benzotriazole Derivatives 1a−f.** Adducts **1a**,**b**[15] and **1d**[16] were prepared by the literature methods quoted. Compounds **1c**,**e**,**f** were synthesized by a procedure[15] similar to that used for **1a**, which was to combine benzotriazole, an aldehyde, and a secondary amine, with azeotropic removal of water in benzene. The crude products **1c**,**e**,**g**,**h**, which were obtained as low melting solids in 80−85% yields with 95−98% purity (as estimated by $^1H$ and $^{13}C$ NMR), were used as such for further reactions.

**Preparation of α-Amino(hetero)arylmethyl Phenols.** Treatment of adducts **1a**−**f** with preformed sodium phenolates **3** in refluxing toluene in the presence of a phase-transfer catalyst (dibenzo-18-crown-6) afforded the corresponding aminoalkylated phenols **6a**−**q** (Scheme 1, Table 1). This synthetic route improved the previously reported[12] yield of compound **6b** from 80% to 87% and extended the methodology to previously unreported derivatives of thiomorpholine **6c**,**i**,**p**. Generally, the yields of the aminoalkylated products **6a**−**p** were 66−88%, independent of the substituents on the benzotriazolyl components **1a**−**f** and phenols **3**. The yields were somewhat higher (82−88%) for the electron-rich 2-naphthols **6a**−**d** and *p*-methoxyphenol **6f**. For compound **6e**, with an electron-donating group on the aldehyde residue, and

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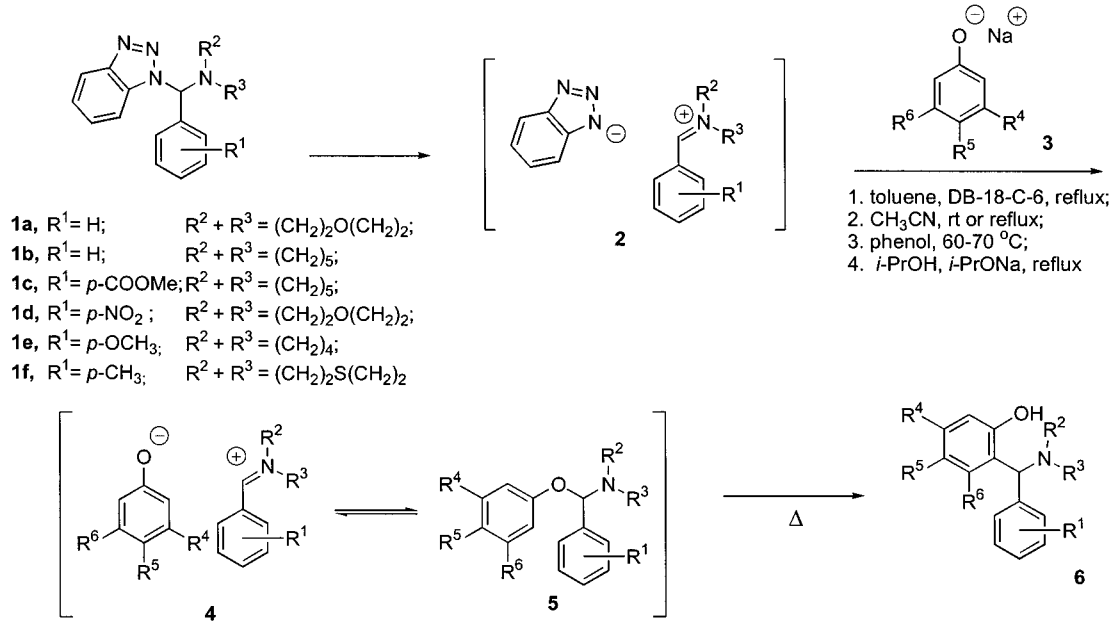
**Scheme 1**[a]

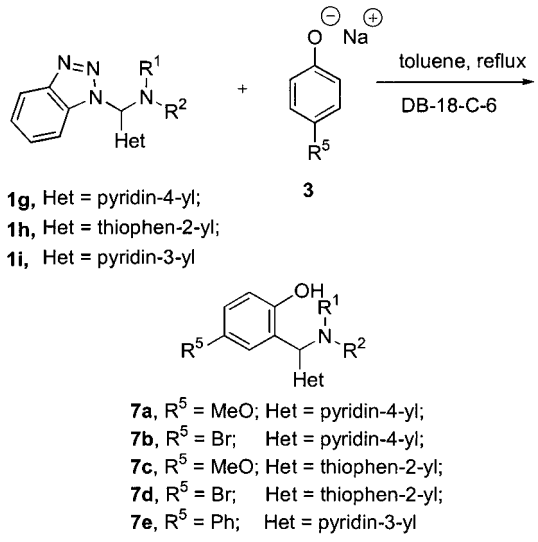



[a] For designation of $R^1$–$R^6$ in **3**–**6** see Table 1.

**Table 1. Amino(benzyl) Phenols 6 via Aminoalkylation with *N*-(α-Aminobenzyl)benzotriazoles**

| entry | Ar | $R^2$, $R^3$ | $R^4$ | $R^5$ | $R^6$ | yield, % |
|---|---|---|---|---|---|---|
| **6a** | Ph | $CH_2CH_2OCH_2CH_2$ | H | CH=CH–CH=CH | | 85 |
| **6b** | Ph | $(CH_2)_5$ | H | CH=CH–CH=CH | | 87 |
| **6c** | Ph | $CH_2CH_2SCH_2CH_2$ | H | CH=CH–CH=CH | | 88 |
| **6d** | *p*-$CH_3OCO-C_6H_4$ | $(CH_2)_5$ | H | CH=CH–CH=CH | | 82 |
| **6e** | *p*-$CH_3O-C_6H_4$ | $(CH_2)_4$ | H | CH=CH–CH=CH | | 74 |
| **6f** | Ph | $CH_2CH_2OCH_2CH_2$ | H | $CH_3O$ | H | 82 |
| **6g** | *p*-$CH_3OCO-C_6H_4$ | $(CH_2)_5$ | H | $CH_3O$ | H | 77 |
| **6h** | Ph | $CH_2CH_2OCH_2CH_2$ | H | Cl | H | 73 |
| **6I** | *p*-$CH_3-C_6H_4$ | $CH_2CH_2SCH_2CH_2$ | H | Br | H | 75 |
| **6j** | Ph | $CH_2CH_2OCH_2CH_2$ | H | H | H | 66 |
| **6k** | Ph | $CH_2CH_2OCH_2CH_2$ | $CH_3$ | H | $CH_3$ | 77 |
| **6l** | Ph | $(CH_2)_5$ | H | $CH_3$ | H | 80 |
| **6m** | Ph | $CH_2CH_2OCH_2CH_2$ | H | $CH(CH_3)_2$ | H | 76 |
| **6n** | Ph | $CH_2CH_2OCH_2CH_2$ | H | $CH_3$ | H | 78 |
| **6o** | Ph | $(CH_2)_5$ | H | Ph | H | 76 |
| **6p** | Ph | $CH_2CH_2OCH_2CH_2$ | H | Ph | H | 72 |
| **6q** | *p*-$NO_2-C_6H_4$ | $CH_2CH_2OCH_2CH_2$ | H | CH=CH–CH=CH | | 51 |

**Scheme 2**




for products **6h**,**g**, derived from phenols with electron-withdrawing groups, the yields were somewhat lower (73–77%). The low 51% yield of the product **6q** can be attributed to the strong electron-withdrawing nature of the nitro group, which can cause phenolic Mannich bases to degrade and form methylenequinones.[7] Methylenequinones were the major products as indicated by our GC/MS experiments and the minor product according to a separate LC/MS experiment performed on the more stable compound **6l**.

**Table 2. Amino(heteroarylmethyl) Phenols 7 via Aminoalkylation with *N*-(α-Aminoheteroarylmethyl)benzotriazoles 1g–e**

| entry | Het | $R^1$, $R^2$ | $R^5$ | yield, % |
|---|---|---|---|---|
| **7a** | pyridin-4-yl | $CH_2CH_2OCH_2CH_2$ | $CH_3O$ | 77 |
| **7b** | pyridin-4-yl | $CH_2CH_2OCH_2CH_2$ | Br | 74 |
| **7c** | thiophen-2-yl | $CH_2CH_2OCH_2CH_2$ | $CH_3O$ | 82 |
| **7c** | thiophen-2-yl | $CH_2CH_2OCH_2CH_2$ | Br | 76 |
| **7c** | pyridin-3-yl | $(CH_2)_5$ | Ph | 75 |

Application of this methodology to heteroaromatic aldehydes allowed the synthesis of previously unreported Mannich-type compounds **7a**–**e** (Scheme 2, Table 2). Compounds **7a**–**e** were obtained smoothly in 74–82% yields, and thus, the general extension of Mannich aminomethylation to amino(hetero)arylmethylation was achieved.

The generation of phenolate anions in situ and the utilization of a more polar media (Scheme 1, entries 2–4)

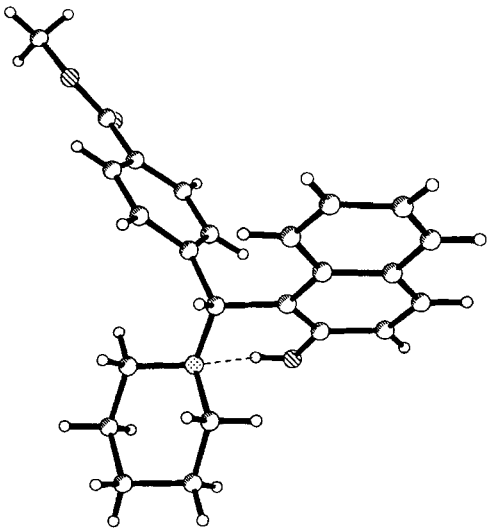


**Figure 1.**

decreased the anion concentration and gave unsatisfactory yields of the desired products**,** which agrees with the results obtained earlier.[12]

Compounds **6a**−**q** were characterized by elemental analysis and $^1$H and $^{13}$C NMR. The interaction of the aryl ring and the naphthol ring in **6a**−**e**,**q** influenced the conformation of the amino ring moiety, as was previously observed for aryl(hydroxynaphthyl)methylpiperidines.[11] This led to the complex broadened NMR lines of the morpholine (**6a**,**q**), piperidine (**6b**,**d**), pyrrolidine (**6e**), and thiomorpholine (**6c**) ring protons resulting from the increase of the inversion barrier of the amino ring. NMR coalescence temperature experiments at 80 °C in DMSO-$d_6$ and X-ray analysis of **6d** (Figure 1) proved that, in addition to the influence of the hydrogen bond, the dynamics of the amino ring in derivatives **6a**−**e**,**q** is restricted by the steric interaction with the aryl ring which is perpendicular to the plane of the naphthol system.

However, the present synthetic method has limitations. First, the procedure reported is limited to secondary aliphatic amines. Primary aliphatic amines are prone to the formation of bis(benzotriazolylalkyl) amines,[15] and the reaction of aniline with benzotriazole and benzaldehyde yielded only the corresponding Schiff base rather than the adduct of type **1**. Second, our syntheses using adducts of benzotriazole, morpholine, and enolizable aliphatic aldehydes such as *i*-butyraldehyde, phenylacetaldehyde, and dihydrocinnamic aldehyde were unsuccessful. We suspect that such adducts, after the formation of intermediates of type **4**, are prone to the loss of the α-proton to yield the corresponding unstable enamine.

In conclusion, we have developed a convenient method for the preparation of aminoalkylated phenols via aminoalkylbenzotriazoles. Compared to the previous methods, this route uses readily available starting materials and gives high yields for various substituted phenols and (hetero)aromatic aldehydes. This provides a new extension of classical Mannich aminomethylation to a variety of (hetero)aromatic aldehydes.

## Experimental Section

**General.** Melting points were determined with a hot-stage apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ with tetramethylsilane as internal standard for $^1$H (300 MHz) or solvent as the internal standard for $^{13}$C (75 MHz). Microanalyses were performed on a Carlo Erba 1106 elemental analyzer. Benzene and toluene were dried over molecular sieves. Column chromatography was conducted with silica gel 200−425 mesh.

The following compounds were prepared according to the procedures described in the literature: 1-morpholino[(phenyl)-methyl]benzotriazole **1a**,[15] 1-piperidino-[(phenyl)methyl] benzotriazole **1b**,[15] and 1-morpholino[(nitrophenyl)methyl] benzotriazole **1d**.[16]

**General Procedure for the Preparation of *N*,*N*-[(Dialkylamino)alkyl]benzotriazoles 1c,e,g−i.** Benzotriazole (50 mmol) and a secondary amine (50 mmol) were mixed in dry benzene (50 mL). The aldehyde (50 mL) was then added, and the mixture was heated at reflux temperature with a Dean−Stark trap until the calculated amount of water (∼0.9 mL) had been collected. The solvent was evaporated under reduced pressure, and the residue was redissolved in methylene chloride (100 mL). The solution was successively washed with 20% sodium carbonate (2 × 30 mL) and water. Evaporation of the methylene chloride after drying over anhydrous $MgSO_4$ gave **1c**,**e**,**g**−**i** with sufficient purity to start the following reaction.

**1-[(4-Methylphenyl)(1,4-thiazinan-4-yl)methyl]benzotriazole (1f) and Its 2-Isomer.** This compound was prepared and purified by recrystallization from 95% ethanol: yield 86%; mp 137−139 °C; $^1$H NMR $\delta$ 8.12−8.10 (m, 1H), 7.91−7.89 (m, 1H), 7.44−7.35 (m, 2H,), 7.26−7.04 (m, 4H), 6.81 (s, 1H); 3.11−2.86 (m, 4H), 2.72−2.61 (m, 4H), 2.36 (s, 3H); $^{13}$C NMR $\delta$ 146.0, 143.8, 138.5, 133.2, 132.7, 131.9, 129.4, 129.1, 127.3, 127.1, 126.4, 123.8, 120.0, 118.4, 111.4, 83.4 [89.6], 51.8 [51.1], 28.0 [28.2], 21.0. Anal. Calcd for $C_{18}H_{20}N_4S$: C, 66.63; H, 6.23; N, 16.95. Found: C, 66.58; H, 6.36; N, 16.95.

**General Procedure for the Preparation of Phenolic Mannich Bases 6a−q and 7a−e.** A mixture of the *N*,*N*-[(dialkylamino)alkyl]benzotriazole derivative (4 mmol) and preformed sodium phenolate (4 mmol) in dry toluene (50 mL) was heated under reflux for 12 h in the presence of a catalytic amount of 18-crown-6. The sodium benzotriazolide was filtered, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel) to give the pure product.

**1-[Morpholino(phenyl)methyl]-2-naphthol (6a).** Hexanes/ethyl acetate (20:1) was used as the eluent to give **6a** in 85% yield as a pale yellow solid, mp 181−183 °C: $^1$H NMR $\delta$ 7.82 (d, $J$ = 8.5 Hz, 1H), 7.68−7.63 (m, 2H), 7.55−7.52 (m, 2H), 7.38−7.10 (m, 6H), 5.09 (s, 1H), 3.78 (br s, 4H), 3.10−2.41 (m, 4H); $^{13}$C NMR $\delta$ 154.7, 138.6, 132.3, 129.7, 129.1, 128.9, 128.8, 128.6, 128.1, 126.5, 122.6, 121.0, 119.8, 115.1, 72.0, 66.8. Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.76; H, 6.56; N, 4.44.

**1-(Phenyl-1-piperidylmethyl)-2-naphthol (6b).** Hexanes/ethyl acetate (20:1) was used as the eluent to give **6b** in 87% yield as a colorless solid, mp 199−201 °C, lit.[10] mp 198 °C: $^1$H NMR $\delta$ 7.85 (d, $J$ = 8.5 Hz, 1H) 7.71−7.65 (m, 2H), 7.59−7.55 (m, 2H), 7.39−7.15 (m, 6H), 5.09 (s, 1H), 3.32−1.21 (m, 10H); $^{13}$C NMR $\delta$ 155.5, 139.7, 132.4, 129.3, 129.2, 129.1, 128.8, 128.6, 127.8, 126.3, 122.3, 121.0, 120.0, 116.1, 72.1, 26.0, 24.1. Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.32; N, 4.41. Found: C, 83.08; H, 7.72; N, 4.45.

**1-[(4-Methylphenyl)(1,4-thiazinan-4-yl)methyl]-2-naphthol (6c).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6c** in 88% yield as colorless prisms, mp 107−109 °C: $^1$H NMR $\delta$ 7.81 (d, $J$ = 8.5 Hz, 1H), 7.66 (t, $J$ = 7.8.Hz, 2H), 7.42−7.33 (m, 3H), 7.20 (d, $J$ = 7.2 Hz, 1H), 7.13 (d, $J$ = 9.0 Hz, 1H), 7.05 (d, $J$ = 7.7 Hz, 2H), 5.13 (s, 1H), 2.69 (br s, 8H), 2.23 (s, 3H); $^{13}$C NMR $\delta$ 154.8, 138.0, 135.5, 132.3, 129.6, 129.1, 129.0, 128.9, 128.8, 128.7, 126.5, 122.5, 121.0, 119.8, 115.6, 71.5, 28.0, 21.0. Anal. Calcd for $C_{22}H_{23}NOS$: C, 75.61, H, 6.63. Found: C, 75.84, H, 6.94. HRMS calcd for $C_{22}H_{23}NOS$: 349.1500, found 349.1687.

**Methyl 4-[(2-Hydroxy-1-naphthyl)(piperidino)methyl]-benzoate (6d).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6d** in 82% yield as colorless prisms, mp 162−163 °C: $^1$H NMR $\delta$ 7.95 (d, $J$ = 7.6 Hz, 2H), 7.81 (d, $J$ = 8.4

Hz, 1H), 7.71−7.65 (m, 4H), 7.37 (t, $J$ = 6.9, 1H), 7.26−7.14 (m, 2H), 5.14 (s, 1H), 3.86 (s, 3H), 3.34−1.33 (m, 10H); $^{13}$C NMR $\delta$ 166.5, 155.5, 144.9, 132.2, 130.0, 129.7, 128.9, 128.6, 126.5, 122.4, 120.7, 120.0, 115.4, 71.6, 52.0., 26.0, 24.0. Anal. Calcd for $C_{24}H_{25}$ $NO_3$: C, 76.80; H, 6.71; N, 3.73. Found: C, 77.20; H, 7.01, N, 3.59.

**1-[(4-Methoxyphenyl)(1-pyrrolidinyl)methyl]-2-naphthol (6e).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6e** in 74% yield as a pale yellow solid, mp 113−115 °C: $^1$H NMR $\delta$ 7.87 (d, $J$ = 8.2 Hz, 1H), 7.70 (t, $J$ = 10.2 Hz, 2H), 7.54 (d, $J$ = 8.0 Hz, 2H), 7.39 (t, $J$ = 6.7 Hz, 1H), 7.26−7.16 (m, 2H), 6.81 (d, $J$ = 7.6 Hz, 2H), 5.1 (s, 1H), 3.74 (s, 3H), 3.28−1.60 (m, 8H); $^{13}$C NMR $\delta$ 159.1, 155.4, 133.5, 131.8, 129.6, 129.3, 128.8, 128.6, 126.3, 122.3, 121.1, 119.9, 116.8, 113.9, 70.0, 55.2, 23.4. Anal. Calcd for $C_{22}H_{23}$ $NO_2$: C, 79.24; H, 6.97; N, 4.20. Found: C, 79.19; H, 6.89; N, 4.22.

**4-Methoxy-2-[morpholino(phenyl)methyl]phenol (6f).** Hexanes/ethyl acetate (10:1) was used as the eluent to give **6f** in 82% yield as colorless prisms, mp 87−89 °C: $^1$H NMR $\delta$ 11.22 (s, 1H), 7.44−7.42 (m, 2H), 7.32−7.26 (m, 3H), 6.81−6.78 (m, 1H), 6.71−6.67 (m, 1H), 6.51 (s, 1H), 4.33 (s, 1H), 3.76−3.69 (m, 4H), 3.67 (s, 3H), 2.60−2.42 (m, 4H);$^{13}$C NMR $\delta$ 152.6, 149.7, 139.2, 128.9, 128.6, 128.1, 125.3, 117.4, 114.9, 113.7, 76.9, 66.8, 55.5, 52.2. Anal. Calcd for $C_{18}H_{21}NO_3$: N, 4.68. Found: N, 4.27. HRMS calcd for $C_{18}H_{21}NO_3$: 299.1521, found 299.1522.

**Methyl 4-[(2-Hydroxy-5-methoxyphenyl)(piperidino)-methyl]benzoate (6g).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6g** in 80% yield as colorless prisms, mp 145−147 °C: $^1$H NMR $\delta$ 11.79 (s, 1H), 7.97 (d, $J$ = 7.5 Hz, 2H), 7.52 (br s, 2H), 6.89 (d, $J$ = 8.7 Hz, 1H), 6.70 (d, $J$ = 8.6 Hz, 1H), 6.46 (s, 1H), 4.43 (s, 1H), 3.90 (s, 3H), 3.66 (s, 3H), 2.52−2.39 (m, 4H), 1.65−1.49 (m, 6H); $^{13}$C NMR $\delta$ 166.7, 152.4, 150.5, 144.8, 130.1, 129.7, 128.6, 125.4, 117.4, 114.8, 113.5, 76.4, 55.6, 52.8, 52.1, 26.0, 24.0. Anal. Calcd for $C_{21}H_{25}NO_4$ N, 3.94. Found: N, 3.95. HRMS calcd for $C_{21}H_{25}$ $NO_4$: 355.1784, found 355.1772.

**4-Chloro-2-[morpholino(phenyl)methyl]phenol (6h).** Hexanes/ethyl acetate (8:2) was used as the eluent to give **6h** in 73% yield as a colorless solid, mp 101−103 °C: $^1$H NMR $\delta$ 11.85 (s, 1H), 7.42−7.28 (m, 5H), 7.10 (d, $J$ = 8.4 Hz, 1H), 6.94 (s, 1H), 6.82 (d, $J$ = 8.5 Hz, 1H), 4.37 (s, 1H), 3.78−3.77 (m, 4H), 2.60−2.44 (m, 4H);$^{13}$C NMR $\delta$ 154.7, 138.3, 129.3, 129.0, 128.9, 128.5, 126.2, 124.0, 118.4, 116.6, 76.2, 66.7, 52.0. Anal. Calcd for $C_{17}H_{18}ClNO_2$: C, 67.21; H, 5.98; N, 4.61. Found: C, 67.27; H, 6.26; N, 4.63.

**4-Bromo-2-[(4-methylphenyl)(1,4-thiazinan-4-yl)methyl]phenol (6i).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6i** in 75% yield as colorless prisms, mp 158−160 °C: $^1$H NMR $\delta$ 11.97 (s, 1H), 7.29−7.17 (m, 5H), 7.02 (s, 1H), 6.77 (d, $J$ = 8.5 Hz, 1H), 4.52 (s, 1H), 2.90−2.55 (m, 8 H), 2.37 (s, 3H); $^{13}$C NMR $\delta$ 155.8, 138.3, 134.4, 131.9, 131.5, 129.7, 128.7, 126.9, 118.8, 111.0, 75.5, 53.0, 28.0, 21.1. Anal. Calcd for $C_{18}H_{20}BrNOS$: C, 57.15; H, 5.33; N, 3.70. Found: C, 57.41; H, 5.69; N, 3.67.

**2-[Morpholino(phenyl)methyl]phenol (6j).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6j** in 66% yield as colorless prisms, mp 117−119 °C: $^1$H NMR $\delta$ 11.72 (s, 1H), 7.43−7.41 (m, 2H), 7.32−7.22 (m, 3H), 7.12 (t, $J$ = 8.0 Hz, 1H), 6.94 (d, $J$ = 7.5 Hz, 1H), 6.86 (d, $J$ = 8.0 Hz, 1H), 6.72 (t, $J$ = 7.4 Hz, 1H), 4.40 (s, 1H), 3.80−3.73 (m, 4H), 2.59−2.42 (m, 4H); $^{13}$C NMR $\delta$ 156.1, 139.3, 129.4, 128.9, 128.7, 128.5, 128.1, 124.8, 119.6, 117.0, 76.8, 66.9, 52.2. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.80; H, 7.12; N, 5.20. Found: C, 75.72; H, 7.14; N, 5.19.

**3,5-Dimethyl-2-[morpholino(phenyl)methyl]phenol (6k).** Hexanes/ethyl acetate (8:2) was used as the eluent to give **6k** in 77% yield as a colorless solid, mp 159−161 °C: $^1$H NMR $\delta$ 12.36 (s, 1H), 7.46 (d, $J$ = 5.5 Hz, 2H), 7.30−7.23 (m, 3H), 6.59 (s, 1H), 6.41 (s, 1H), 4.49 (s, 1H), 3.75 (br s, 4H), 3.10−2.34 (m, 4H), 2.21 (s, 3H), 2.14 (s, 3H);$^{13}$C NMR $\delta$ 156.4, 138.5, 138.4, 136.6, 129.2, 128.8, 128.0, 122.7, 120.3, 115.8, 72.6, 66.8, 52.6, 21.0, 19.7. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73, H, 7.80, N, 4.71. Found: C, 76.55, H, 7.86, N, 4.67.

**4-Methyl-2-[phenyl(piperidino)methyl]phenol (6l).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6l** in 80% yield as colorless prisms, mp 117−119 °C, lit.[10] mp 112 °C: $^1$H NMR $\delta$ 12.25 (s, 1H), 7.41 (br s, 2H) 7.33−7.26 (m, 3H), 6.91 (d, $J$ = 8.2 Hz, 1H), 6.77 (d, $J$ = 7.9 Hz, 2H), 4.38 (s, 1H), 2.45−2.29 (m, 4H) 2.15 (s, 3H), 1.64−1.46 (m, 6H); $^{13}$C NMR $\delta$ 154.5, 140.0, 129.6, 128.8, 128.7, 128.0, 127.8, 125.4, 116.6, 111.2, 76.7, 52.7, 26.1, 24.2, 20.5. Anal. Calcd for $C_{19}H_{23}$-NO: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.01; H, 8.30; N, 4.98.

**4-Isopropyl-2-[morpholino(phenyl)methyl]phenol (6m).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6m** in 76% yield as colorless prisms, mp 91−93 °C: $^1$H NMR $\delta$ 11.44 (s, 1H), 7.45−7.43 (m, 2H), 7.34−7.27 (m, 3H), 7.00 (d, $J$ = 6.8 Hz, 1H), 6.79 (d, $J$ = 8.2 Hz, 2H), 4.37 (s, 1H), 3.76−3.74 (m, 4H), 2.75−2.71 (m, 1H), 2.69−2.42 (m, 4 H), 1.14 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR $\delta$ 153.8, 139.8, 139.5, 128.8, 128.0, 127.3, 126.3, 124.3, 116.7, 77.0, 66.9, 52.3, 33.1, 24.2, 24.0. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.11; N, 4.50. Found: C, 77.30; H, 8.51; N, 4.64.

**4-Methyl-2-[morpholino(phenyl)methyl]phenol (6n).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6n** in 78% yield as a colorless solid, mp 87−88 °C: $^1$H NMR $\delta$ 11.45 (s, 1H), 7.45−7.43 (m, 2H), 7.33−7.26 (m, 3H), 6.93 (d, $J$ = 8.2 Hz, 1H), 6.79−6.76 (m, 2H), 4.33 (s, 1H), 3.80−3.75 (m, 4H), 2.60−2.17 (m, 4H), 2.17 (s, 3H); $^{13}$C NMR $\delta$ 153.5, 139.6, 129.8, 129.2, 128.9, 128.6, 128.5, 128.0, 124.5, 116.8, 77.0, 66.9, 52.4, 20.4. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.48; N, 4.94. Found: C, 76.46; H, 7.19; N, 4.92.

**3-[Phenyl(piperidino)methyl][1,1-biphenyl]-4-ol (6o).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6o** in 76% yield as colorless prisms, mp 132−134 °C: $^1$H NMR $\delta$ 12.70 (s, 1H), 7.45−7.20 (m, 11H), 7.13 (s, 1H), 6.92 (d, $J$ = 8.3 Hz, 1H), 4.52 (s, 1H), 2.44−2.30 (m, 4H), 1.67−1.27 (m, 6H);$^{13}$C NMR $\delta$ 156.8, 141.0, 139.5, 132.1, 128.7, 128.6, 127.9, 127.0, 126.5, 126.3, 125.8, 117.3, 76.7, 52.6, 26.1, 24.1. Anal. Calcd for $C_{24}H_{25}NO$: C, 83.92; H, 7.35; N, 4.08. Found: C, 83.70; H, 7.51; N, 4.05

**4-Phenyl-2-[(4-methylphenyl)(1,4-thiazinan-4-yl)methyl]phenol (6p).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6p** in 72% yield as colorless prisms, mp 169−171 °C: $^1$H NMR $\delta$ 11.89 (s, 1H), 7.43−7.23 (m, 7H), 7.20−7.13 (m, 4H), 6.94−6.92 (d, $J$ = 8.3 Hz, 1H), 4.60 (s, 1H), 2.85−2.75 (m, 8H), 2.31 (s, 3H); $^{13}$C NMR $\delta$ 156.2, 140.8, 138.0, 135.2, 132.5, 129.6, 128.78, 128.6, 128.1, 127.2, 126.5, 126.4, 125.1, 117.4, 76.2, 53.2, 28.1, 21.1. Anal. Calcd for $C_{24}H_{25}NOS$: N, 3.73. Found: N, 3.52. HRMS calcd for $C_{24}H_{25}NOS$: 375.1657, found 375.1651.

**1-[Morpholino(4-nitrophenyl)methyl]-2-naphthol (6q).** Hexanes/ethyl acetate (9:1) was used as the eluent to give **6q** in 51% yield as a yellow solid, mp 177−179 °C: $^1$H NMR $\delta$ 12.81 (s,1H), 8.12(d, $J$ = 8.2 Hz, 2H), 7.79(d, $J$ = 5.6, 3H), 7.71 (d, $J$ = 2.3 Hz, 2H), 7.42 (t, $J$ = 7.2 Hz, 1H), 7.26 (t, $J$ = 7.4 Hz, 1H), 7.16 (d, $J$ = 8.9 Hz, 1H), 5.24 (s, 1H), 3.82−3.70 (m, 4H), 3.12−2.44 (m, 4H); $^{13}$C NMR $\delta$ 154.7, 147.6, 146.1, 131.9, 130.5, 129.8, 129.1, 128.9, 127.0, 124.2, 123.0, 120.3, 119.8, 113.8, 71.0, 66.7. Anal. Calcd for $C_{21}H_{20}N_2O_4$: N, 7.69. Found: N, 7.72.

**4-Methoxy-2-[morpholino(4-pyridinyl)methyl]phenol (7a).** Chloroform/methanol (50:1) was used as the eluent to give **7a** in 78% yield as a yellow solid, mp 148−150 °C: $^1$H NMR $\delta$ 10.72 (s, 1H), 8.50 (d, $J$ = 5.2 Hz, 2H), 7.34 (d, $J$ = 5.2 Hz, 2H), 6.76 (d, $J$ = 8.8 Hz, 1H), 6.69−6.65 (m, 1H), 6.47 (d, $J$ = 2.5 Hz, 1H), 4.24 (s, 1H), 3.71 (br s, 4H), 3.64 (s, 3H), 2.68−2.48 (m, 2H), 2.48−2.36 (m, 2H); $^{13}$C NMR $\delta$ 152.8, 150.4, 149.4, 148.0, 123.8, 123.1, 117.7, 114.6, 114.2, 75.9, 66.6, 55.6, 52.3. Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.88; H, 6.88; N, 9.30.

**4-Bromo-2-[morpholino(4-pyridinyl)methyl]phenol (7b).** Chloroform/methanol (100:1) was used as the eluent to give **7b** in 74% yield as a yellow solid, mp 175−177 °C: $^1$H NMR $\delta$ 11.40 (s, 1H), 8.56 (d, $J$ = 4.5 Hz, 2H), 7.37 (d, $J$ = 4.8 Hz, 2H), 7.24 (d, $J$ = 8.6 Hz, 1H), 7.11 (s, 1H), 6.77 (d, $J$ = 8.7 Hz, 1H), 4.35 (s, 1H), 3.75 (br s, 4H), 2.70−2.50 (m, 2H), 2.50−2.40 (m, 2H); $^{13}$C NMR $\delta$ 155.0, 150.4, 147.4, 131.9, 131.4,

125.4, 122.9, 119.0, 111.3, 74.6, 66.4, 52.1. Anal. Calcd for $C_{16}H_{17}BrN_2O_2$: C, 55.03; H, 4.92; N, 8.02. Found: C, 54.99; H, 4.86; N, 7.94.

**4-Methoxy-2-[morpholino(2-thienyl)methyl]phenol (7c).** Chloroform/hexanes (9:1) was used as the eluent to give **7c** in 82% yield as an oil: $^1$H NMR $\delta$ 10.8 (br s, 1H), 7.28−7.25 (m, 1H), 7.11 (d, $J$ = 2.4 Hz, 1H), 6.97−6.94 (m, 1H), 6.84−6.72 (m, 3H), 6.57 (s, 1H) 4.70 (s, 1H), 3.78 (s, 4H), 3.71 (s, 3H), 2.62−2.50 (m, 4H); $^{13}$C NMR $\delta$ 149.4, 141.1, 127.0, 126.7, 126.1, 125.2, 117.5, 116.0, 114.8, 114.0, 70.6, 66.8, 55.6, 51.6. Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.58. Found: C, 63.10; H, 6.56; N, 4.18.

**4-Bromo-2-[morpholino(2-thienyl)methyl]phenol (7d).** Chloroform/hexanes (9:1) was used as the eluent to give **7d** in 76% yield as a yellow solid, mp 122−124 °C: $^1$H NMR $\delta$ 11.39 (s, 1H), 7.26−7.23 (m, 2H), 7.09 (br s, 2H), 6.98−6.95 (m, 1H), 6.76 (d, $J$ = 8.7 Hz, 1H), 4.70 (s, 1H), 3.76 (br s, 4H), 2.59−2.48 (m, 4H); $^{13}$C NMR $\delta$ 155.1, 140.3, 131.9, 131.6, 127.3, 126.9, 126.7, 126.3, 118.9, 111.2, 70.1, 66.8, 51.6. Anal. Calcd for $C_{15}H_{16}BrNO_2S$: C, 50.86; H, 4.55; N, 3.95. Found: C, 51.22; H, 4.53; N, 3.88.

**3-[Piperidino(3-pyridinyl)methyl][1,1′-biphenyl]-4-ol (7e).** Chloroform/hexanes (10:1) was used as the eluent to give **7e** in 75% yield as a yellow solid, mp 65−67 °C: $^1$H NMR $\delta$ 12.34 (br s, 1H), 8.63 (s, 1H), 8.53 (d, $J$ = 4.1 Hz, 1H), 7.84 (d, $J$ = 7.2 Hz, 1H), 7.44−7.23 (m, 7H), 7.10 (s, 1H), 6.95 (d, $J$ = 8.2 Hz, 1H), 4.56 (s, 1H), 2.45−2.36 (m, 4H), 1.80−1.60 (m, 6H); $^{13}$C NMR $\delta$ 156.3, 149.7, 149.2, 140.3, 135.6, 134.9, 132.1, 128.4, 127.3, 127.1, 126.2, 126.1, 124.7, 123.6, 117.3, 73.4, 52.3, 25.7, 23.6. Anal. Calcd for $C_{23}H_{24}N_2O$: N, 8.13. Found: N, 7.76.

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