Syntheses of Oxazabicycle Library via One-Pot Tandem Reactions

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Received January 5, 2008

A practical protocol for the preparation of a parallel solution-phase library of oxazabicycle is reported. Target compounds were obtained in moderate to good yields by a $Yb(OTf)_3$-catalyzed one-pot tandem reaction from various anisidines, aromatic aldehydes, isobutyraldehyde, and 4-hydroxycoumarins/dimedone. Purification of the final products by either recrystallization in ethyl acetate/methylene chloride or column chromatography allowed easy isolation of the 18 components of the array.

Introduction

Molecules with functional groups having cleft-like shapes have emerged as a useful tool for molecular recognition studies for the past decade. For instance, the rigid clefts derived from Troger's base **1** (Figure 1),[1] a concave chiral diamine with a perpendicular arrangement of two aromatic rings, have been used as hosts in molecular recognition,[2] DNA intercalation,[3] and enzyme inhibition[4] and as ligands for asymmetric catalysis.[5] Recently, several new cleftlike heterobicycles have been synthesized, and their unique properties have been reported. To name a few, the dioxabicycle **2** has been evaluated to be a moderate inhibitor for the enzyme vitamin K 2,3-epoxide reductase;[6] the oxazabicycle **3** has been found to be the first example of the bicycle-based photochromic colorant.[7] In light of the aforementioned multifunctional properties and potential biological activity associated with the oxazabicyclic moiety, we envisioned that an efficient preparation of the oxazabicyclic derivatives with diverse substitution patterns may facilitate the exploration of their unprecedented properties. Multicomponent reactions (MCRs)[8] represent an attractive synthetic strategy for rapid and efficient library generation because the products are formed in a single step and the diversity can be achieved simply by varying the reaction components; therefore, here we report our efforts toward the development of a facile, atom-economical, solution-phase parallel synthetic protocol to diversify the oxazabicyclic scaffold in three different positions using an MCR-like tandem methodology.

Results and Discussion

Figure 2 shows the four commercially available components used to build up the oxazabicyclic skeleton, which include anisidine, aromatic aldehyde, isobutyraldehyde, and 4-hydroxycoumarin.

The target oxazabicycles were obtained, as indicated in Scheme 1, in a one-pot tandem reaction by first mixing *p*-anisidine with aromatic aldehyde, isobutyraldehyde, and 0.4 equiv of ytterbium trifluoromethanesulfonate ($Yb(OTf)_3$) in 1,2-dichloroethane at room temperature for 12 h. 4-Hydroxycoumarin was then added, and the solution was refluxed for 3 h. After the reaction was quenched with water, the products were extracted with methylene chloride, dried in $MgSO_4$, concentrated in vacuo, and subsequently purified by recrystallization in ethyl acetate/methylene chloride or flash column chromatography. Figure 3 shows the structures of 18 compounds from the generated array with the yield given underneath, which demonstrated the versatility of this one-pot tandem reaction through the four-component preparation of a small library of oxazabicycles. It can be observed that the one-pot tandem reaction gave better yields (ranging from 58 to 70%) for aromatic aldehydes with an electron-withdrawing group like nitro or trifluoromethyl at the para position and for 4-hydroxycoumarins with an electron-donating *N*,*N*-dimethylamino group at the 7-position. Conversely, the aromatic aldehydes with a substituent at the ortho position resulted in lower yields, presumably, because of the unfavorable steric hindrance occurred during the coupling reactions. The starting material 4-hydroxy-7-*N*,*N*-dimethylaminocoumarin[9] and 4-methoxynaphthalen-1-amine[10] used for the synthesis of compounds **7f−j** and **7n−o** were prepared according to the literature procedure. Not surprisingly, replacement of anisidine with bulkier 4-methoxynaphthalen-1-amine also resulted in lower yields of **7n−o**. It is noteworthy that no product was obtained when isobutyraldehyde was replaced with 2-ethylbutanal or cyclohexanecarbaldehyde, which implies that increasing bulkiness of isobutyraldehyde may impede the final cyclization step of the reactions.

Scheme 2 shows the proposed mechanism for this programmed one-pot tandem synthesis.[11] It began with an equilibrium-driven condensation of *p*-anisidine and furan-2-carbaldehyde in 1,2-dichloroethane to afford the imine **4**. The second step involved a nonequilibrium, $Yb(OTf)_3$-catalyzed coupling of **4** with isobutyraldehyde to give the cyclized aminoalcohol **5**.[12] Final reacting of **5** with 4-hydroxycoumarin under reflux conditions yielded the speculated coupled **6** and subsequently cyclized **7a**.[13] The fact that no

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10.1021/cc8000025 CCC: $40.75
Published on Web 03/08/2008

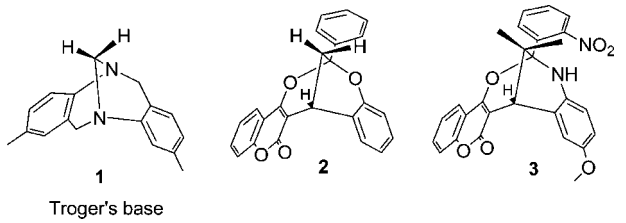


Figure 1. Some heterobicyclic derivatives that possess biological activities and other properties.

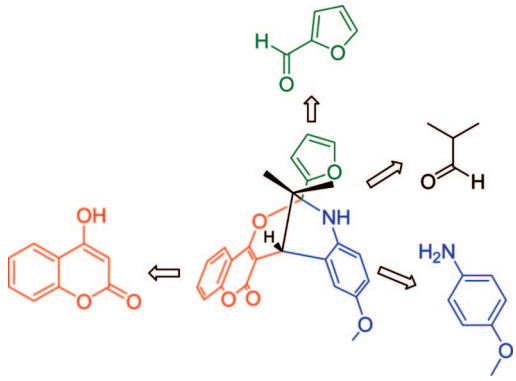
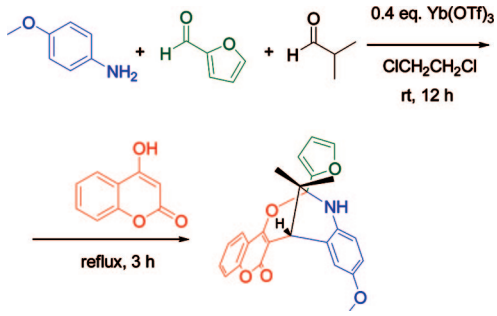


Figure 2. Components used for the synthesis of the oxazabicycles.

Scheme 1. Preparation of the Oxazabicycle Using a Four-Component Reaction



product formed when amino alcohol **5** was refluxed with 4-hydoxycoumarin in the absence of $Yb(OTf)_3$ suggested that the aforementioned reactions were all Lewis acid-catalyzed, including the last coupling and cyclization steps. When 4-hydroxycoumarin was replaced with the less reactive dimedone, the byproduct **8** was isolated (Scheme 2). This observation indicated that the unconsumed anisidine in the solution may compete with dimedone to react with the aminoalcohol **5** to yield the undesired amine **8**, which resulted in the low yields of **7k**−**m**. It is noteworthy that the bond formation during the construction of the bicyclic skeleton was highly efficient and atom-economical, with a total mass loss of only 38 g/mol, that is, the release of two molecules of water and one molecule of hydrogen. The structural assignment of the prepared oxazabicycles was based on spectroscopic data (^{1}H, ^{13}C NMR, HRMS). In the ^{1}H NMR spectra, a characteristic bridgehead hydrogen absorption peak for the oxazabicyclic ring was observed at the chemical shifts between 3.67 and 3.81 ppm for all prepared compounds. Some of the heterobicyclic structures were further elucidated by the X-ray crystallography.

Figure 4 shows the ORTEP diagrams of the oxazabicycles **7a** and **7f**, which clearly reveal a rigid oxazabicyclo[3.3.1] skeleton.[14] Presumably, this Lewis acid-catalyzed one-pot tandem reaction can be expanded to prepare other heterobicyclic compounds like diazabicycles by simply replacing the last added component to the appropriate 4-alkylaminocoumarins.

Conclusions

In summary, a practical and straightforward parallel solution-phase synthesis of oxazabicycles using a $Yb(OTf)_3$-catalyzed, one-pot tandem reaction is developed. Purification of the final products can be accomplished by either recrystallization in ethyl acetate/methylene chloride or column chromatography with moderate to good yields. Our protocol for this four-component reaction provides a quick access to the oxazabicycles with diverse substitution patterns from readily available precursors. Further studies of the photophysical property and biological activity for this library are currently ongoing.

Experimental Section

Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz on a Varian VXR300 spectrometer. Chemical shifts were reported in parts per million on the δ scale relative to an internal standard (tetramethylsilane or appropriate solvent peaks) with coupling constants given in hertz. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). MS were performed on a JEOL JMS-SX/SX 102A spectrometer. IR spectra were obtained using a 1725XFT-IR spectrophotometer. Single-crystal structures were determined by a Bruker AXS SMART-1000 X-ray single-crystal diffractometer. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60H) by elution with the solvent systems. Solvents, unless otherwise specified, were reagent grade and were distilled once prior to use.

General Procedure. To a solution of *p*-anisidine (1.0 mmol), aromatic aldehyde (1.0 mmol), isobutyraldehyde (1.0 mmol), and a catalytic amount of $Yb(OT_f)_3$ (0.4 mmol) in 1,2-dichloroethane (10 mL) were added, and the mixture was stirred at room temperature for 12 h. 4-Hydroxycoumarin (1.0 mmol) was added to the mixture, and the resulting solution was refluxed for 3 h. After the mixture was cooled down to room temperature, the reaction was quenched with water (10 mL). The product was then extracted twice with methylene chloride (25 mL each). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting crude product was recrystallized in methylene chloride/ethyl acetate (1:6) or purified by column chromatography (1:9 EtOAc/hexanes) to give a target product.

Preparation of 7a: white solid; yield 47%; mp 299−301 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (dd, J = 7.8, 1.2 Hz, 1H), 7.55 (dd, J = 1.8, 0.9 Hz, 1H), 7.47 (ddd, J = 8.7, 7.2, 1.5 Hz, 1H), 7.28−7.20 (m, 2H), 7.08 (d, J = 2.7 Hz, 1H), 6.69 (dd, J = 3.3, 0.9 Hz,1H), 6.62 (dd, J = 8.7, 3.3

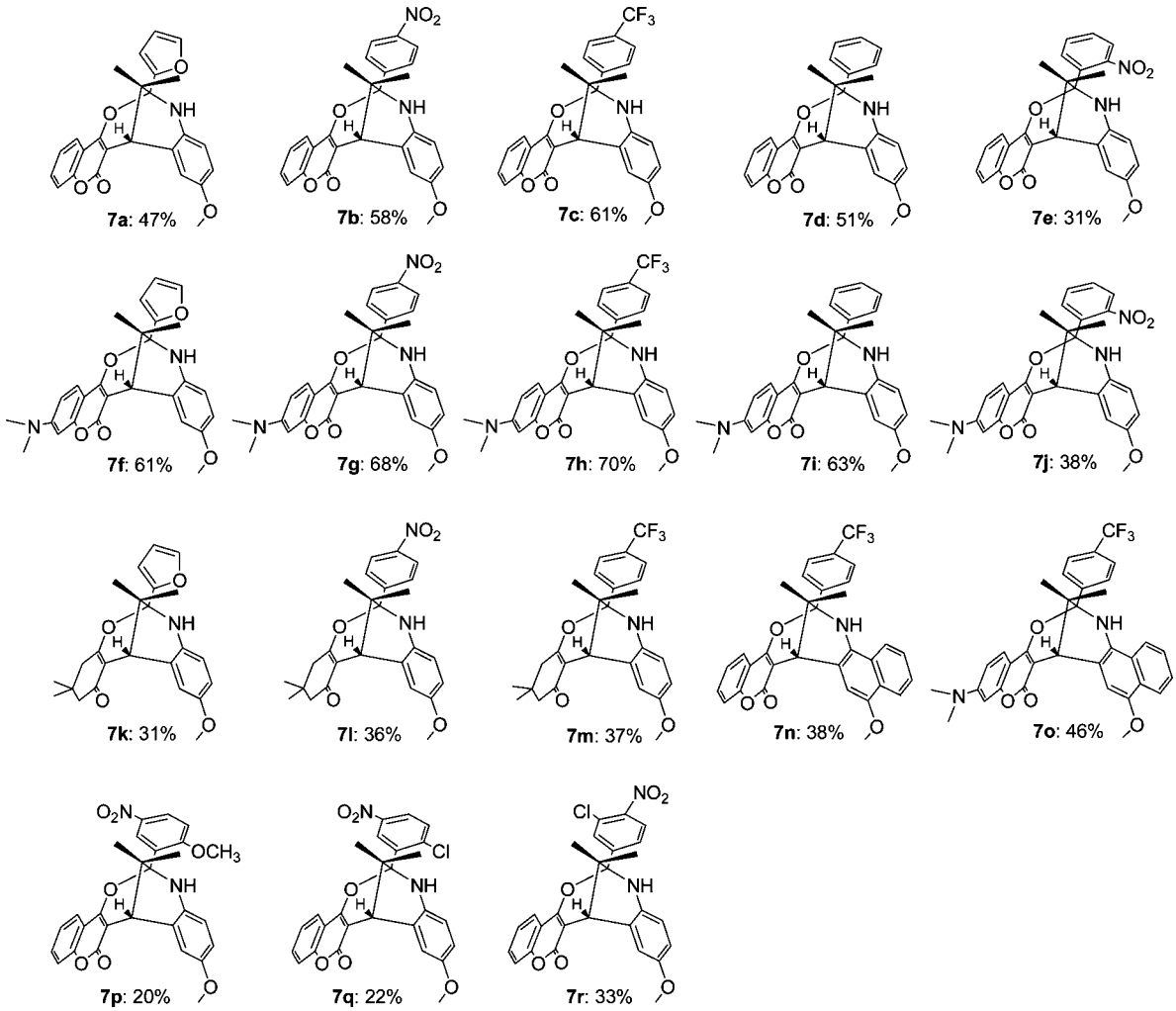
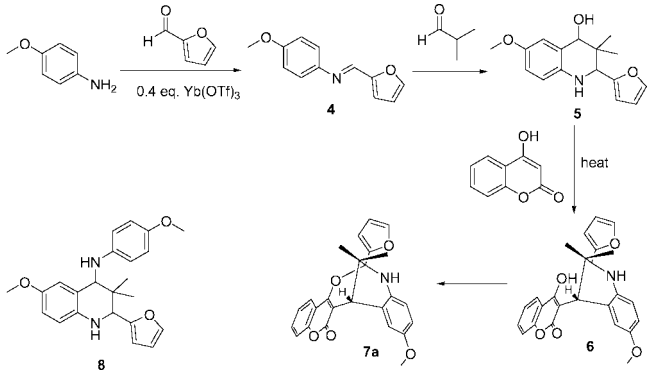


Figure 3. Library products **7a**–**r** obtained by a parallel four-component tandem reaction.

Scheme 2. Proposed Mechanism for the Formation of the Oxazabicycle **7a** and the Byproduct **8**



Hz, 1H), 6.53−6.51 (m, 2H), 5.18 (s, 1H), 3.83 (s, 1H), 3.77 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.5, 159.4, 153.4, 152.4, 150.9, 143.5, 132.5, 131.8, 125.4, 123.9, 123.2, 116.8, 115.7, 114.0, 113.8, 111.2, 111.0, 105.9, 56.0, 42.2, 33.7, 22.9, 22.4; IR ν (KBr) 3324, 2993, 1690, 1626, 1502 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{25}H_{21}NO_5$ 415.1420, found 415.1426 (M^+).

Preparation of 7b: yellow solid; yield 58%; mp 313−315 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33 (d, J = 9.0 Hz, 2H), 7.98 (d, J = 9.0 Hz, 2H), 7.82 (dd, J = 7.2, 1.2 Hz, 1H), 7.52 (ddd, J = 8.1, 7.2, 1.8 Hz, 1H), 7.32−7.26 (m, 2H), 7.09 (d, J = 3.0 Hz, 1H), 6.65 (dd, J = 8.7, 3.0 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 5.01 (s, 1H), 3.85 (s, 1H), 3.78 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.0, 158.9, 153.5, 152.2, 148.4, 145.2, 132.4, 131.8, 129.9, 125.4, 123.9, 123.1, 122.6, 116.8, 115.2, 114.2, 113.8, 113.7, 105.9, 96.0, 55.8, 42.0, 33.3, 22.8, 22.1; IR ν (KBr) 3394, 2934, 1702, 1349, 1247, 1038 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{27}H_{22}N_2O_6$ 470.1478, found 470.1480 (M^+).

Preparation of 7c: white solid; yield 61%; mp 278−279 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91 (d, J = 8.1 Hz, 2H), 7.82 (dd, J = 7.5, 1.5 Hz, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.51 (ddd, J = 8.1, 7.2, 1.5 Hz, 1H), 7.31−7.24 (m, 2H), 7.08 (d, J = 2.4 Hz, 1H), 6.64 (dd, J = 8.4, 2.7 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 4.98 (s, 1H), 3.83 (s, 1H), 3.78 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1, 159.2, 153.2, 152.2, 151.8, 142.2, 132.7, 131.6, 129.2, 125.3, 124.9, 123.8, 122.6, 116.7, 115.3, 114.1, 114.0, 113.6, 105.8, 96.2, 55.7, 42.0, 33.1, 22.8, 22.1; IR ν (KBr) 3327, 2937, 1690, 1627, 1504, 1326 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{28}H_{22}F_3NO_4$ 493.1501, found 493.1507 (M^+).

Preparation of 7d: white solid; yield 51%; mp 287−289 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, J = 7.8 Hz, 1H), 7.77−7.73 (m, 2H), 7.50−7.44 (m, 4H), 7.26 (d, J =

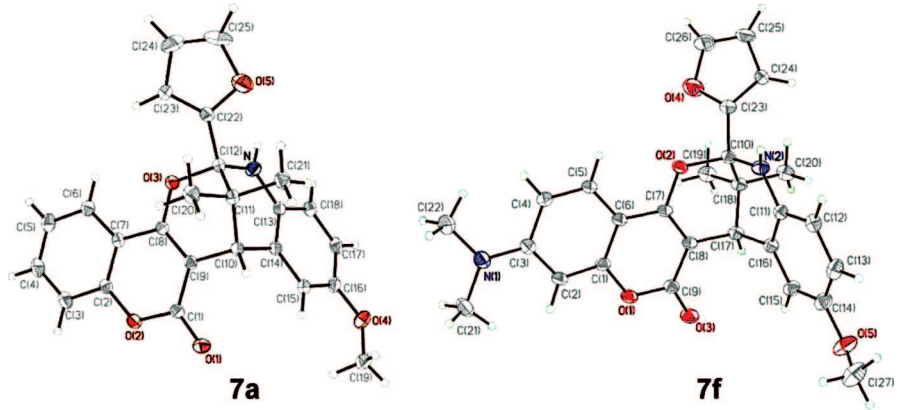


Figure 4. X-ray crystal structures of the oxazabicycles **7a** and **7f**.

8.4 Hz, 1H), 7.20 (d, J = 8.1 Hz, 1H), 7.09 (d, J = 3.0 Hz, 1H), 6.63 (dd, J = 8.4, 3.0 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 5.01 (s, 1H), 3.81 (s, 1H), 3.77 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3, 159.6, 152.9, 152.2, 138.2, 133.1, 131.5, 129.0, 128.6, 128.0, 125.3, 123.7, 122.8, 116.6, 115.6, 113.7, 113.6, 113.5, 105.7, 96.7, 55.7, 42.1, 33.0, 22.9, 22.1; IR ν (KBr) 3337, 2989, 1690, 1628, 1503, 1040 cm^{-1}; HRMS (EI) m/z calcd for $C_{27}H_{23}NO_4$ 425.1627, found 425.1617 (M^+).

Preparation of 7e: yellow solid; yield 31%; mp 258−259 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89−7.86 (m, 1H), 7.76 (dd, J = 8.4, 1.2 Hz, 1H), 7.62−7.59 (m, 2H), 7.52−7.43 (m, 2H), 7.28 (ddd, J = 8.4, 7.5, 1.2 Hz, 2H), 7.05 (d, J = 2.7 Hz, 1H), 6.63 (dd, J = 8.7, 2.7 Hz, 1H), 6.51 (d, J = 8.7 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 1H), 1.14 (s, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.0, 158.6, 153.5, 152.2, 151.2, 132.2, 131.7, 130.6, 129.6, 129.0, 125.4, 124.1, 124.0, 123.0, 116.5, 115.2, 114.0, 113.65, 113.60, 106.0, 55.7, 42.3, 34.6, 23.7, 23.0; IR ν (KBr) 3351, 3000, 1689, 1624, 1539, 1502, 1382, 1247, 1045, 828 cm^{-1}; HRMS (EI) m/z calcd for $C_{27}H_{22}N_2O_6$ 470.1478, found 470.1476 (M^+).

Preparation of 7f: white solid; yield 61%; mp 317−319 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (d, J = 9.0 Hz, 1H), 7.53 (dd, J = 1.5, 0.9 Hz, 1H), 7.08 (d, J = 2.7 Hz, 1H), 6.67 (dd, J = 3.3, 0.9 Hz, 1H), 6.61 (dd, J = 8.4, 2.7 Hz, 2H), 6.56 (dd, J = 9.0, 2.7 Hz, 1H), 6.52−6.49 (m, 2H), 6.44 (d, J = 2.4 Hz, 1H), 5.10 (s, 1H), 3.77 (s, 4H), 3.01 (s, 6H), 1.06 (s, 3H), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.4, 160.0, 154.1, 152.9, 152.8, 151.2, 143.0, 132.4, 125.9, 123.5, 117.6, 113.6, 113.5, 113.3, 110.6, 108.5, 101.0, 97.7, 92.4, 55.7, 41.8, 40.1, 33.4, 22.7, 22.1; IR ν (KBr) 3290, 2936, 1682, 1606, 1501, 1404 cm^{-1}; HRMS (EI) m/z calcd for $C_{27}H_{26}N_2O_5$ 458.1842, found 458.1835 (M^+).

Preparation of 7g: yellow solid; yield 68%; mp 348−349 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (d, J = 9.0 Hz, 2H), 7.96 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 2.7 Hz, 1H), 6.66−6.55 (m, 3H), 6.45 (d, J = 2.4 Hz, 1H), 4.96 (s, 1H), 3.78 (s, 3H), 3.73 (s, 1H), 3.03 (s, 6H), 1.00 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.8, 159.6, 154.1, 153.1, 152.1, 148.0, 145.5, 133.8, 130.6, 125.5, 123.4, 122.6, 113.7, 112.1, 108.9, 105.0, 103.6, 100.8, 97.3, 96.0, 54.9, 54.5, 41.8, 32.7, 22.4, 21.5; IR ν (KBr) 3386, 2935, 1693, 1617, 1504, 1348 cm^{-1}; HRMS (EI) m/z calcd for $C_{29}H_{27}N_3O_6$ 513.1900, found 513.1903 (M^+).

Preparation of 7h: white solid; yield 70%; mp 287−288 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 9.0 Hz, 1H), 7.09 (d, J = 3.0 Hz, 1H), 6.63 (dd, J = 8.4, 3.0 Hz, 1H), 6.58 (dd, J = 8.7, 2.4 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 4.91 (s, 1H), 3.80 (s, 1H), 3.78 (s, 3H), 3.03 (s, 6H), 0.99 (s, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.0, 159.9, 154.2, 153.0, 152.8, 142.7, 132.7, 129.2, 126.1, 124.8, 123.2, 114.7, 113.8, 113.5, 113.3, 108.5, 104.1, 101.1, 97.8, 95.4, 55.7, 41.8, 40.1, 33.2, 22.9, 22.0. IR ν (KBr) 3280, 2935, 1685, 1326, 1125 cm^{-1}; HRMS (EI) m/z calcd for $C_{30}H_{27}F_3N_2O_4$ 536.1923, found 536.1922 (M^+).

Preparation of 7i: white solid; yield 63%; mp 321−322 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73−7.70 (m, 2H), 7.54 (d, J = 8.7 Hz, 1H), 7.49−7.44 (m, 3H), 7.09 (d, J = 2.7 Hz, 1H), 6.63 (dd, J = 8.7, 2.7 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.44−6.38 (m, 2H), 4.90 (s, 1H), 3.77 (s, 3H), 3.75 (s, 1H), 2.99 (s, 6H), 0.96 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.3, 153.1, 152.7, 148.5, 147.5, 138.6, 133.2, 128.8, 128.6, 127.9, 126.1, 123.4, 113.5, 113.4, 113.2, 108.4, 104.4, 101.1, 97.8, 95.8, 55.7, 42.0, 40.1, 33.1, 22.9, 22.1; IR ν (KBr) 3340, 2938, 1680, 1608, 1502, 1403 cm^{-1}; HRMS (EI) m/z calcd for $C_{29}H_{28}N_2O_4$ 468.2049, found 468.2052 (M^+).

Preparation of 7j: yellow solid; yield 38%; mp 270−271 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88−7.85 (m, 1H), 7.60−7.57 (m, 2H), 7.53 (d, J = 9.0 Hz, 1H), 7.44−7.41 (m, 1H), 7.05 (d, J = 2.7 Hz, 1H), 6.63−6.58 (m, 2H), 6.50 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 1H), 3.01 (s, 6H), 1.11 (s, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.9, 159.4, 154.1, 153.4, 152.9, 151.2, 132.24, 132.18, 130.4, 129.54, 129.48, 126.2, 124.0, 123.6, 113.8, 113.5, 113.3, 108.8, 104.1, 101.2, 97.8, 55.7, 42.1, 40.1, 34.7, 23.9, 23.1; IR ν (KBr) 3279, 2907, 1680, 1533, 1399, 1188 cm^{-1}; HRMS (EI) m/z calcd for $C_{29}H_{27}N_3O_6$ 513.1900, found 513.1903 (M^+).

Preparation of 7k: white solid; yield 31%; mp 274−276 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49 (dd, J = 1.8, 0.9 Hz, 1H), 6.92 (d, J = 3.0 Hz, 1H), 6.58 (dd, J = 8.4, 3.0 Hz, 1H), 6.55 (dd, J = 3.3, 0.9 Hz, 1H), 6.48 (d, J = 8.4 Hz, 1H), 6.45 (dd, J = 3.3, 1.8 Hz, 1H), 4.98 (s, 1H), 3.74 (s, 3H), 3.67 (s, 1H), 2.34, 2.26 (Abq, J = 17.4 Hz, 1H each), 2.18 (s, 2H), 1.07 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.3, 168.2,

152.7, 151.4, 143.0, 132.6, 126.6, 114.8, 113.8, 113.2, 112.7, 110.5, 110.4, 92.0, 55.7, 50.4, 41.9, 39.8, 32.9, 32.5, 29.5, 27.4, 22.5, 22.2; IR ν (KBr) 3448, 3223, 1630, 1545, 1345 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{24}H_{27}NO_4$ 393.1940, found 393.1942 (M^+).

Preparation of 7l: yellow solid; yield 36%; mp 261−262 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.27 (d, J = 9.0 Hz, 2H), 7.86 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 3.0 Hz, 1H), 6.61 (dd, J = 8.4, 3.0 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 4.78 (s, 1H), 3.75 (s, 3H), 3.68 (s, 1H), 2.39, 2.31 (Abq, J = 18.4 Hz, 1H each), 2.21 (s, 2H), 1.11 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.0, 167.9, 153.0, 148.1, 145.9, 132.7, 129.8, 126.8, 122.7, 115.1, 113.8, 113.6, 112.8, 94.7, 55.7, 50.4, 41.9, 39.9, 32.8, 32.6, 29.3, 27.6, 22.8, 22.1; IR ν (KBr) 3337, 1602, 1351, 1248, 1039 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{26}H_{28}N_2O_5$ 448.1998, found 448.1991 (M^+).

Preparation of 7m: white solid; yield 37%; mp 235−237 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 2.4 Hz, 1H), 6.68−6.53 (m, 2H), 5.00 (s, 1H), 3.71 (s, 3H), 3.67 (s, 1H), 2.37, 2.29 (Abq, J = 19.2 Hz, 1H each), 2.16 (s, 2H), 1.09 (s, 3H), 0.98 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.1, 168.3, 152.6, 142.7, 133.0, 129.1, 126.6, 126.0, 124.5, 114.9, 113.6, 113.3, 112.7, 94.9, 55.5, 50.3, 41.9, 39.9, 32.6, 32.5, 29.4, 27.4, 22.7, 22.0; IR ν (KBr) 3282, 2962, 1616, 1504, 1326 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{27}H_{28}F_3NO_3$ 471.2021, found 471.2025 (M^+).

Preparation of 7n: white solid; yield 38%; mp 301−302 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.25 (dd, J = 7.8, 1.5 Hz, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.85−7.81 (m, 1H), 7.80 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.1 Hz, 1H), 7.50−7.42 (m, 3H), 7.30−7.24 (m, 2H), 7.06 (s, 1H), 5.44 (s, 1H), 4.02 (s, 3H), 3.98 (s, 1H), 1.08 (s, 3H), 1.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.4, 159.5, 152.2, 149.2, 142.5, 131.7, 131.6, 131.1, 129.5, 126.8, 126.1, 125.0, 124.8, 123.9, 123.1, 122.8, 122.6, 119.8, 119.0, 116.8, 115.3, 106.5, 105.6, 96.2, 55.9, 42.4, 33.4, 22.9, 22.2. IR ν (KBr) 3394, 2934, 1702, 1349, 1247, 1038 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{32}H_{24}F_3NO_4$ 543.1657, found 543.1660 (M^+).

Preparation of 7o: white solid; yield 46%; mp 327−328 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, J = 1.8 Hz, 1H), 8.03 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 9.0 Hz, 1H), 7.50−7.38 (m, 2H), 7.08 (s, 1H), 6.55 (dd, J = 9.0, 2.4 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 5.38 (s, 1H), 4.01 (s, 3H), 3.91 (s, 1H), 3.00 (s, 6H), 1.04 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.3, 160.3, 154.2, 152.9, 149.0, 142.9, 131.3, 130.9, 129.5, 126.6, 125.9, 124.94, 124.89, 124.8, 124.6, 123.2, 123.0, 122.9, 120.7, 119.0, 108.6, 105.7, 104.1, 101.8, 97.9, 95.5, 55.9, 42.2, 40.2, 33.5, 23.0, 22.2; IR ν (KBr) 3317, 2914, 1681, 1616, 1405, 1323 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{34}H_{29}F_3N_2O_4$ 586.2079, found 586.2075 (M^+).

Preparation of 7p: yellow solid; yield 20%; mp 309−310 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.78 (d, J = 3.0 Hz, 1H), 8.36 (dd, J = 9.0, 3.0 Hz, 1H), 7.83 (dd, J = 7.8, 1.2 Hz, 1H), 7.53−7.47 (m, 1H), 7.30−7.24 (m, 2H), 7.13 (d, J = 9.3 Hz, 1H), 7.09 (d, J = 3.0 Hz, 1H), 6.66 (dd, J = 8.7, 3.0 Hz, 1H), 6.51 (d, J = 8.7 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 1H), 3.79 (s, 3H), 1.04 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.7, 162.3, 158.7, 153.1, 152.3, 141.1, 133.0, 131.6, 129.9, 128.1, 127.9, 126.6, 126.1, 124.6, 123.9, 122.8, 116.6, 115.6, 113.9, 113.6, 113.0, 112.3, 105.1, 56.5, 55.8, 42.4, 43.6, 22.8, 22.4. IR ν (KBr) 3374, 2968, 1691, 1617, 1502 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{28}H_{24}N_2O_7$ 500.1584, found 500.1582 (M^+).

Preparation of 7q: yellow solid; yield 22%; mp 305−306 °C; ^1H NMR ($CDCl_3$,300 MHz) δ 8.88 (d, J = 2.7 Hz, 1H), 8.25 (dd, J = 8.7, 2.7 Hz, 1H), 7.83 (dd, J = 8.1, 1.2 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.55−7.49 (m, 1H), 7.32−7.25 (m, 2H), 7.09 (d, J = 2.7 Hz, 1H), 6.68 (dd, J = 8.7, 2.7 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 3.83 (s, 1H), 3.79 (s, 3H), 2.05 (s, 1H), 1.12 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.0, 158.3, 153.5, 152.3, 146.2, 140.7, 136.7, 134.0, 131.9, 131.8, 128.0, 125.0, 124.7, 124.0, 123.0, 116.7, 115.4, 113.9, 113.7, 113.6, 105.5, 60.4, 55.8, 42.4, 35.6, 23.1, 22.7; IR ν (KBr) 3388, 2939, 1692, 1574, 1528, 1459, 1389, 1349, 1248, 1041, 753 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{27}H_{21}ClN_2O_6$ 504.1088, found 504.1079 (M^+).

Preparation of 7r: yellow solid; yield 33%; mp 294−295 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.31 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 8.4, 2.1 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.85 (dd, J = 8.1, 1.8 Hz, 1H), 7.81 (s, 1H), 7.63−7.57 (m, 1H), 7.39−7.35 (m, 2H), 6.83 (d, J = 2.7 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 6.61 (dd, J = 8.7, 2.7 Hz, 1H), 5.74 (s, 1H), 3.72 (s, 1H), 3.65 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.3, 159.1, 152.1, 151.8, 147.4, 138.9, 134.6, 133.8, 132.5, 131.5, 126.3, 126.1, 125.0, 124.6, 123.2, 116.6, 115.0, 114.2, 114.0, 112.7, 105.7, 55.5, 55.2, 41.6, 32.7, 22.5, 21.6. IR ν (KBr) 3331, 2966, 1695, 1624, 1504, 1386, 1248 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{27}H_{21}ClN_2O_6$ 504.1088, found 504.1086 (M^+).

Supporting Information Available. Spectral data for **7a**−**r** and the X-ray crystallographic data for **7a** and **7f**. This information is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgment. The authors would like to thank the National Science Council of the Republic of China, Taiwan, for financially supporting this research under Contract No. NSC 95-2113-M-029-001.

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(14) Crystallographic data (excluding structure factors) for compounds **7a** and **7f** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-664284 and -671994, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K., fax +44 1223 336033.

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