Solid-Phase Synthesis of Linked Heterocycles from a Selenopolystyrene Resin

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A linked heterocycle library of isoxazoles, 1,2,3-triazoles, bicyclo[2.2.1]hepta-2,5-diene or 4-methylcyclohexa-1,3-diene and 1,2,4-oxadiazoles was prepared by solid-phase organic synthesis. Key steps on resin-bound selenium were electrophilic additions; 1,3-dipolar cycloaddition; Porco's two-step, one-pot condensation of amidoxime and carboxylate; and Diels−Alder reaction.

Introduction

Combinatorial chemistry has become a highly powerful tool in drug discovery,[1] and solid-phase organic synthesis (SPOS) is one of the core technologies used for synthesis of compound libraries.[2] Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. As a result, the field of solid-phase heterocyclic chemistry has rapidly expanded for the preparation of pharmaceutically useful heterocyclic compounds.[3]

Isoxazoles and oxadiazoles are present in various biologically active compounds, since isoxazoles are readily transformed into various biodynamic agents, including those with antithrombotic, PAF antagonist, and hypolipidemic properties.[4] Oxadiazoles are important bioisosters for esters and amides in drug discovery with reported muscarinic agonist, benzodiazepine receptor agonist, 5-HT agonist, and antirhinoviral activities.[5] Triazole, substituted bicyclo[2.2.1]hepta-2,5-dienes and 4-methylcyclohexa-1,3-dienes also play important roles as pharmacophores in many pharmaceuticals.[6] They have also been used in asymmetric catalysis.[7] Therefore, they are all interesting targets that can be made, potentially, through solid-phase chemistry.

The first organoselenium resin[8] was reported in 1976, and in 1998, Nicolaou[9a] and Ruhland[9b] reported the development of organoselenium resins for their versatile reactivities. Recently, others[10] and our research group[11] have been interested in the preparation of heterocyclic libraries from organoselenium resins. Herein, we present our investigation of the applicability of SPOS methodology for the preparation of a linked heterocyclic library of isoxazoles, 1,2,3-triazoles, bicyclo[2.2.1]hepta-2,5-diene, or 4-methylcyclohexa-1,3-diene, and 1,2,4-oxadiazoles, with the advantages of straightforward synthetic operation, lack of odor and good stability of the supported selenium species, and high purities of the products.

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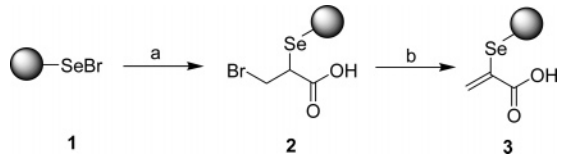
Scheme 1[a]



[a] Reagents and conditions: (a) CH_2=CHCOOH (5.0 equiv), $ZnCl_2$ (0.1 equiv), CH_2Cl_2, r.t., 2.0 h.; (b) *t*-BuONa (4.0 equiv), anhydrous Et_2O, r.t., 12 h.

Results and Discussion

Polystyrene-supported selenenyl bromide **1**[9] (dark-red resin, Br: 1.02 mmol/g) was chosen as the starting material. It was found that in the presence of 10 mol % $ZnCl_2$, resin **1** could react with acrylic acid smoothly, and the dark-red resin changed to pale yellow after stirring for 2 h, FTIR showed a strong carbonyl absorption at 1712 cm^{-1}, and prolonging the reaction time did not increase this. Resin **2** was then reacted with *t*-BuONa to give the corresponding yellow resin **3** almost quantitatively (Br was undetectable through microanalysis of resin **3**), and the carboxylate loading of resin **3** was determined by acid−base titration[11e,12] to be 0.99 mmol/g (Scheme 1).

With resin **3** in hand, two choices existed (route A or route B) to allow construction of the linked heterocyclic product **6** through 1,3-dipolar cycloaddition reaction[13] and Porco's two-step, one-pot condensation[14] (Scheme 2).

In route A, a 1,3-dipolar cycloaddition reaction was performed on resin **3** to furnish the resin-bound 3-substituted 4,5-dihydroisoxazol **4.** Resin **4** was then reacted with amidoxime and DCC using Porco's two-step, one-pot condensation to give the resin-bound biheteroaryl **5**, which was followed by selenoxide syn elimination to give the substituted 5-(isoxazol-5-yl)-1,2,4-oxadiazole **6**. In route B, resin **3** reacted with amidoxime in the presence of DCC to give the resin-bound 3-substituted -5-vinyl-1,2,4-oxadiazole **7** initially, which then reacted with nitrile oxides through a 1,3-dipolar cycloaddition to furnish the resin-bound biheteroaryl **5**.

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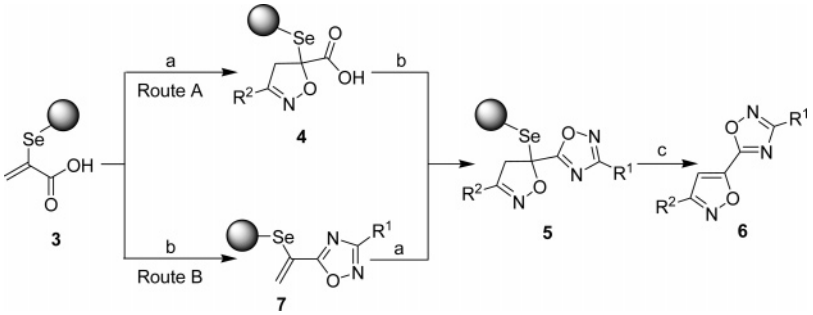
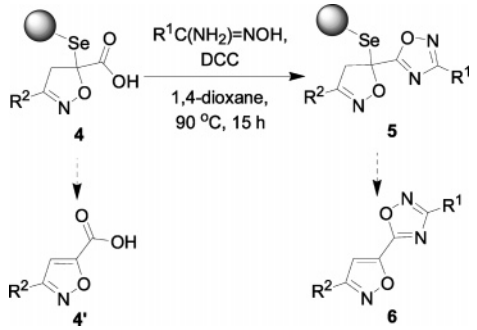
Scheme 2[a]



[a] Reagents and conditions: (a) $R^2CH{=}NOH$, NCS, CH_2Cl_2, Et_3N, r.t., 24 h; (b) DCC, $R^1C(NH_2){=}NOH$, 1,4-dioxane. 90 °C, 15 h; (c) H_2O_2, THF, 0 °C, 30 min, then r.t., 20 min.

Scheme 3



Although the purity of the linked heterocycles **6** is good through either route A or route B, the yields were different. The yield of product **6** obtained through route B was higher than that through route A. Upon further investigation, it was found that resins **4** and **5** could undergo cleavage and aromatization to form the 3-substituted isoxazole-5-carboxylic acid **4′** and the substituted 5-(isoxazol-5-yl)-1,2,4-oxadiazole **6** (Scheme 3).

Therefore, we chose route B. The results are described in Table 1 and show that the linked heterocycles **6** could be obtained in moderate to good yield with high purities. The structure of **6j** was established by X-ray diffraction studies (Figure 1).

In addition to nitrile oxides, azides can perform 1,3-dipolar cycloadditions easily. In the presence of CuI and proline, resin **7** reacted smoothly with aryl halides and sodium azide through a one-pot, 1, 3-dipolar cycloaddition[15] to furnish the resin-bound biheteroaryl **8**, which was followed by selenoxide syn elimination to give the substituted 4-(1,2,4-oxadiazol-5-yl)-1*H*-1,2,3-triazole **9** (Scheme 4). The results are presented in Table 2.

To expand the diversity of this method, Diels−Alder reactions were tested.[16] Cyclopentadiene was initially used as a diene to perform the Diels−Alder reaction on resin **7**, but low conversion was observed when the reaction was catalyzed by $ZnCl_2$.[17] Further investigation showed that the use of other solvents, such as THF, toluene, CH_2Cl_2, and acetone, did not improve the yield of the desired product. Fortunately, the use of 1.2 equiv of ZnI_2 as the catalyst in DCM resulted in the formation of the desired adduct in good yield. Resin **10** was then treated with H_2O_2 to give the substituted 5-(bicyclo[2.2.1]hepta-2,5-dien-2-yl)-1,2,4-oxadiazole **11** in good yields and high purities (Scheme 5, Table 3).

Table 1. Synthesis of the Substituted 5-(Isoxazol-5-yl)-1,2,4-oxadiazole

product	R^1	R^2	yield (%)[a]	purity (%)[b]	route
6a	C_6H_5	4-$CH_3C_6H_4$	51	92	A
6a	C_6H_5	4-$CH_3C_6H_4$	73	92	B
6b	4-ClC_6H_4	4-$CH_3C_6H_4$	66	91	B
6c	C_6H_5	4-$CH_3OC_6H_4$	64	89	B
6d	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	65	92	B
6e	4-BrC_6H_4	4-$CH_3OC_6H_4$	60	91	B
6f	4-ClC_6H_4	4-$CH_3OC_6H_4$	61	94	B
6g	4-FC_6H_4	4-$CH_3OC_6H_4$	58	93	B
6h	2-ClC_6H_4	4-$CH_3OC_6H_4$	59	94	B
6i	C_6H_5	C_6H_{11}	76	93	B
6j	4-$CH_3C_6H_4$	C_6H_{11}	74	95	B
6k	4-BrC_6H_4	C_6H_{11}	71	92	B
6l	4-ClC_6H_4	C_6H_{11}	71	90	B
6m	2-ClC_6H_4	C_6H_{11}	67	95	B
6n	3-BrC_6H_4	C_6H_{11}	55	91	A
6n	3-BrC_6H_4	C_6H_{11}	70	91	B
6o	C_6H_5	4-ClC_6H_4	71	88	B
6p	4-$CH_3C_6H_4$	4-ClC_6H_4	68	90	B
6q	4-BrC_6H_4	4-ClC_6H_4	63	95	B
6r	4-ClC_6H_4	4-ClC_6H_4	61	90	B
6s	C_6H_5	2-ClC_6H_4	58	90	B
6t	4-$CH_3C_6H_4$	2-ClC_6H_4	59	93	B
6u	4-FC_6H_4	2-ClC_6H_4	56	88	B
6v	4-$CH_3C_6H_4$	4-$NO_2C_6H_4$	48	87	B
6w	C_6H_5	COOEt	70	90	B

[a] Yield of the crude product based on the loading of resin **1**. [b] Purity of the crude product was determined by HPLC (λ = 254 nm).

The use of isoprene in place of cyclopentadiene gave the substituted 5-(4-methylcyclohexa-1,3-dienyl)-1,2,4-oxadiazole **13** (Scheme 6, Table 4).

Conclusions

In summary, we have developed an efficient solid-phase parallel synthetic route to a bis-heterocycle library of isoxazoles, 1,2,3-triazoles, bicyclo[2.2.1]hepta-2,5-diene or 4-methylcyclohexa-1,3-diene, and 1,2,4-oxadiazoles using a polymer-supported seleno resin. The advantages of this method include straightforward operation, lack of odor and good stability of the supported selenium species, and the high purities of the products.

Experimental Section

General Methods. Starting materials were obtained from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone immediately

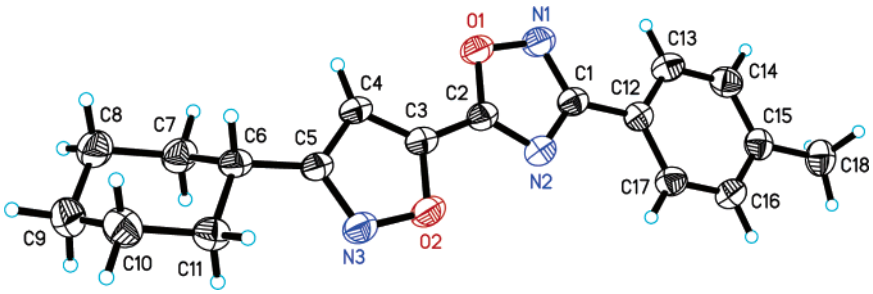
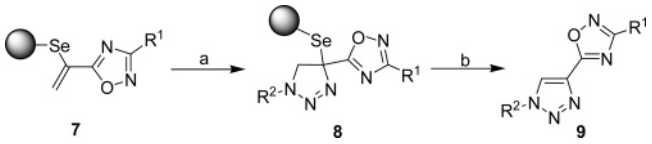


Figure 1. X-ray crystal structure of **6j**.

Scheme 4 [a]



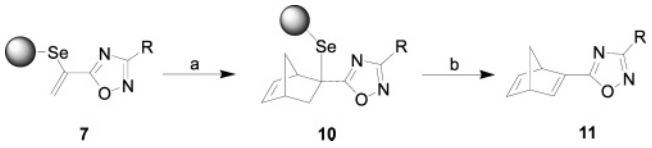
[a] Reagents and conditions: (a) NaN_3, R^2I, CuI, proline, LiOH, DMSO, 65 °C, 15 h; (b) H_2O_2, THF, 0 °C, 30 min, then r.t., 40 min.

Table 2. Synthesis of the Substituted 4-(1,2,4-Oxadiazol-5-yl)-1*H*-1,2,3-triazole

product	R^1	R^2	yield (%)[a]	purity (%)[b]
9a	C_6H_5	C_6H_5	68	89
9b	4-$CH_3C_6H_4$	C_6H_5	66	90
9c	4-BrC_6H_4	C_6H_5	60	89
9d	4-ClC_6H_4	C_6H_5	61	92
9e	4-FC_6H_4	C_6H_5	58	89
9f	2-ClC_6H_4	C_6H_5	59	91
9g	3-BrC_6H_4	C_6H_5	60	91
9h	C_6H_5	4-$CH_3C_6H_4$	60	91
9i	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	61	91
9j	4-BrC_6H_4	4-$CH_3C_6H_4$	58	89
9k	3-BrC_6H_4	4-$CH_3C_6H_4$	58	88
9l	C_6H_5	2-$CH_3C_6H_4$	62	90
9m	4-$CH_3C_6H_4$	2-$CH_3C_6H_4$	60	89
9n	4-BrC_6H_4	2-$CH_3C_6H_4$	59	93
9o	2-ClC_6H_4	2-$CH_3C_6H_4$	56	90

[a] Yield of the crude product based on the loading of resin **1**. [b] Purity of the crude product was determined by HPLC (λ = 254 nm).

Scheme 5 [a]



[a] Reagents and conditions: (a) cyclopentadiene, ZnI_2, CH_2Cl_2, r.t., 12 h; (b) H_2O_2, THF, 0 °C, 20 min, then r.t., 1.0 h.

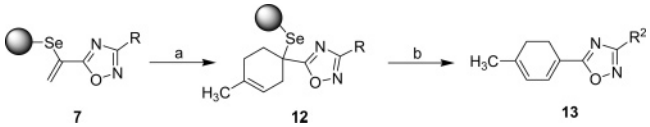
prior to use. Polystyrene (H 1000, 100−200 mesh, cross-linked with 1% divinylbenzene) was used for the preparation of selenenyl bromide resin (1.02 mmol of Br/g) according to the procedure described by Nicolaou and co-workers[10] and was purchased from commercial sources (Nankai University). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance spectrometer using $CDCl_3$ as the solvent and TMS as an internal standard. Mass spectra (EI, 70 eV) were recorded on a HP5989B mass spectrometer. Infrared spectra were recorded on a Shimadzu IR-408 spectrometer. Elemental analyses were performed on a Flash EA1112 instrument. HPLC was performed on an Agilent 1100 (column, Eclipse XDB-C18 5 μm, 4.6 × 150 mm; mobile phase, THF/MeOH/H_2O, 50/20/30 (v/v); flow rate, 1.0 mL/min; detector, UV 254 nm). The samples were further purified by TLC for ^{13}C NMR and microanalysis.

Table 3. Synthesis of the Substituted 5-(Bicyclo[2.2.1]-hepta-2,5-dien-2-yl)-1,2,4-oxadiazole

product	R	yield (%)[a]	purity (%)[b]
11a	C_6H_5	78	90
11b	4-$CH_3C_6H_4$	78	91
11c	4-$CH_3OC_6H_4$	77	92
11d	4-BrC_6H_4	73	91
11e	4-ClC_6H_4	74	95
11f	4-FC_6H_4	71	87
11g	2-ClC_6H_4	68	92
11h	3-BrC_6H_4	73	89

[a] Yield of the crude product based on the loading of resin **1**. [b] Purity of the crude product was determined by HPLC (λ = 254 nm).

Scheme 6 [a]



[a] Reagents and conditions: (a) isoprene, ZnI_2, CH_2Cl_2, r.t., 48 h; (b) H_2O_2, THF, 0 °C, 20 min, then r.t., 40 min.

Table 4. Synthesis of the Substituted 5-(4-Methylcyclohexa-1,3-dienyl)-1,2,4-oxadiazole

product	R	yield (%)[a]	purity (%)[b]
13a	C_6H_5	73	94
13b	4-$CH_3C_6H_4$	74	92
13c	4-$CH_3OC_6H_4$	74	91
13d	4-BrC_6H_4	69	90
13e	4-ClC_6H_4	70	89
13f	4-FC_6H_4	64	90
13g	2-ClC_6H_4	59	88
13h	3-BrC_6H_4	65	91

[a] Yield of the crude product based on the loading of resin **1**. [b] Purity of the crude product was determined by HPLC (λ = 254 nm).

Typical Procedure for the Preparation of Resin-Bound Acrylic Acid 3. To a suspension of the swollen resin **1** (1.0 g, 1.02 mmol of Br/g) in CH_2Cl_2 (10 mL) was added $ZnCl_2$ (0.10 mmol). After 10 min with stirring at room temperature, acrylic acid (5 mmol) was added, and the mixture was stirred for 2.0 h. The resin was collected on a filter and washed successively with H_2O (20 mL × 2), THF (10 mL × 2), acetone (10 mL × 2), THF/H_2O (2:1) (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) and then dried under vacuum overnight to afford resin **2**.

t-BuONa (4.0 mmol) was added to a suspension of the swollen resin **2** in anhydrous diethyl ether (20 mL), and the mixture was stirred for 12 h at room temperature. Resin was collected by filtration, washed with H_2O (20 mL × 2), THF/H_2O (2:1) (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) and then dried in a vacuum overnight to afford resin **3**.

Typical Procedure for the Titration of Carboxylate of Resin 3. Titration was effected by treating 0.5 g of resin **3** with an excess of *n*-BuLi in benzene and back-titrating with 0.1 N HCl. Resin **3** was found to contain around 0.99 mmol of functional group/g.

Typical Procedure for the Preparation of Resin-Bound 3-Substituted -5-Vinyl-1,2,4-Oxadiazole 7. Under a positive pressure of nitrogen, to a suspension of the swollen polystyrene resin **3** (1.0 g) in anhydrous 1,4-dioxane (15 mL) was added DCC (3.5 mmol) and amidoxime (3.0 mmol). The mixture was stirred at 90 °C for 15 h. Resin 7 was collected by filtration; washed with hot DMF (10 mL × 3), hot THF (10 mL × 3), hot EtOH (10 mL × 3), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2); and then dried in a vacuum.

Typical Procedure for the Preparation of the Substituted 5-(Isoxazol-5-yl)-1,2,4-Oxadiazole 6 (Products 6a−v). Under a positive pressure of nitrogen, to a suspension of the swollen resin **7** (0.6 g) in CH_2Cl_2 (15 mL) was added a solution of hydroximoyl halide (2.5 mmol) in CH_2Cl_2 (10 mL) (prepared from 2.5 mmol of aldoxime and 2.5 mmol of NCS in CH_2Cl_2 (15 mL) stirring at room temperature for 4 h before use). A solution of Et_3N (5 mmol) in CH_2Cl_2 (15 mL) was slowly added dropwise in three portions every 8 h (each time, 1.66 mmol in anhydrous CH_2Cl_2 (5 mL) was added). After stirring for 24 h at room temperature, resin **5** was collected by filtration; washed with DMF (10 mL × 3), THF (10 mL × 2), ether (10 mL × 2), THF/H_2O (2:1) (10 mL × 2), H_2O (10 mL × 2), THF (10 mL × 2), benzene (10 mL × 2), and CH_2Cl_2 (10 mL × 2).

The washed resin **5** was suspended in THF (15 mL), 30% (aq) H_2O_2 (0.5 mL) was added, and the mixture was stirred for 30 min at 0 °C, followed by 40 min at room temperature. The mixture was filtered, and the resin was washed with CH_2Cl_2 (15 mL × 2). The filtrate was washed with H_2O (30 mL × 2), dried over $MgSO_4$, and evaporated to dryness under vacuum to obtain the crude products **6**. Further purification was via flash chromatography with *n*-hexanes/EtOAc (8:1 v/v) as the eluent for ^{13}C NMR and microanalysis.

6a. White solid, mp: 191−193 °C. ^1H NMR ($CDCl_3$) δ 8.20−8.18 (2H, m,), 7.80 (2H, d, J = 8.0 Hz), 7.56−7.54 (3H, m), 7.47 (1H, s), 7.34 (2H, d, J = 8.0 Hz), 2.44 (3H, s); ^{13}C NMR ($CDCl_3$) δ 169.3, 165.4, 163.2, 155.7, 141.2, 131.8, 129.9, 129.0, 127.7, 126.9, 125.9, 124.7, 106.3, 21.5; MS *m*/*z* 158 (100), 303 (M^+); IR ν_{max} (cm^{-1}) 2924, 2854, 1651, 1513, 1428, 1357, 1112, 898, 824, 743, 695. Anal. Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28%; H, 4.32%; N, 13.85%. Found: C, 71.17%; H, 4.39%; N, 13.90%.

6b. White solid, mp: 200−202 °C. ^1H NMR ($CDCl_3$) δ 8.14 (2H, d, J = 8.4 Hz), 7.80 (2H, d, J = 8.0 Hz), 7.53 (2H, d, J = 8.4 Hz), 7.47 (1H, s), 7.34 (2H, d, J = 8.0 Hz), 2.44 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.5, 165.5, 163.2, 155.4, 141.2, 138.0, 129.9, 129.4, 129.0, 126.9, 124.5, 124.3, 106.4, 21.5; MS *m*/*z* 158 (100), 337 (M^+); IR ν_{max} (cm^{-1}) 2924, 1655, 1604, 1509, 1429, 1410, 1351, 1094, 1017837, 819, 756. Anal. Calcd for $C_{18}H_{12}ClN_3O_2$: C, 64.01%; H, 3.58%; N, 12.44%. Found: C, 64.09%; H, 3.54%; N, 12.38%.

6c. White solid, mp: 124−126 °C. ^1H NMR ($CDCl_3$) δ 9.23 (1H, s), 8.09−8.07 (2H, m), 7.90 (2H, d, J = 8.8 Hz), 7.53−7.49 (3H, m), 7.05 (2H, d, J = 8.8 Hz), 3.89 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.7, 168.6, 162.3, 161.5, 159.7, 131.5, 130.9, 128.9, 127.5, 126.3, 118.8, 114.0, 106.7, 55.4; MS *m*/*z* 173 (100), 319 (M^+); IR ν_{max} (cm^{-1}) 3098, 2932, 1645, 1613, 1447, 1358, 1254, 1137, 956, 823, 751,690. Anal. Calcd for $C_{18}H_{13}N_3O_3$: C, 67.71%; H, 4.10%; N, 13.16%. Found: C, 67.62%; H, 4.16%; N, 13.11%.

6d. White solid, mp: 126−128 °C. ^1H NMR ($CDCl_3$) δ 9.21 (1H, s), 7.97 (2H, d, J = 8.0 Hz), 7.89 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.05 (2H, d, J = 8.8 Hz), 3.89 (3H, s), 2.42 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.6, 168.3, 162.2, 161.4, 159.6, 141.8, 130.9, 129.6, 127.4, 123.4, 118.8, 113.9, 106.7, 55.3, 21.5; MS *m*/*z* 173 (100), 333 (M^+); IR ν_{max} (cm^{-1}) 2925.1644, 1616, 1425, 1253, 1137, 873, 823, 759. Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46%; H, 4.54%; N, 12.61%. Found: C, 68.58%; H, 4.49%; N, 12.56%.

6e. Pale yellow solid, mp: 160−162 °C. ^1H NMR ($CDCl_3$) δ 9.25 (1H, s), 7.96 (2H, d, J = 8.8 Hz), 7.87 (2H, d, J = 8.8 Hz), 7.65 (2H, d, J = 8.8 Hz), 7.05 (2H, d, J = 8.8 Hz), 3.90 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.8, 168.0, 162.3, 161.5, 159.7, 132.2, 130.9, 129.0, 126.1, 125.2, 118.7, 114.0, 106.5, 55.4; MS *m*/*z* 173 (100), 397 (M^+), 399 (M + 2); IR ν_{max} (cm^{-1}) 3123, 2924, 1643, 1616, 1474, 1405, 1253, 1143, 798, 760. Anal. Calcd for $C_{18}H_{12}BrN_3O_3$: C, 54.29%; H, 3.04%; N, 10.55%. Found: C, 54.22%; H, 3.09%; N, 10.51%.

6f. White solid, mp: 170−172 °C. ^1H NMR ($CDCl_3$) δ 9.24 (1H, s), 8.03 (2H, d, J = 8.4 Hz), 7.87 (2H, d, J = 8.4 Hz), 7.48 (2H, d, J = 8.4 Hz), 7.05 (2H, d, J = 8.4 Hz), 3.90 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.8, 167.9, 162.3, 161.5, 159.7, 137.7, 130.9, 129.3, 124.8, 118.8, 114.0, 106.6, 55.4; MS *m*/*z* 173 (100), 353 (M^+); IR ν_{max} (cm^{-1}) 3115, 2937, 1646, 1510, 1409, 1356, 1255, 1137, 834, 759. Anal. Calcd for $C_{18}H_{12}ClN_3O_3$: C, 61.11%; H, 3.42%; N, 11.88%. Found: C, 61.02%; H, 3.46%; N, 11.85%.

6g. White solid, mp: 150−151 °C. ^1H NMR ($CDCl_3$) δ 9.24 (1H, s), 8.10−8.07 (2H, m), 7.88 (2H, d, J = 8.8 Hz), 7.20−7.16 (2H, m), 7.06 (2H, d, J = 8.8 Hz), 3.90 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.7, 167.9, 164.7 (J = 249.9 Hz), 162.3, 161.5, 159.7, 130.9, 129.7 (J = 8.9 Hz), 122.5 (J = 3.9 Hz), 118.8, 116.2 (J = 22.0 Hz), 114.0, 106.6, 55.4; MS *m*/*z* 173 (100), 337 (M^+); IR ν_{max} (cm^{-1}) 3128, 2925, 1609, 1523, 1420, 1260, 1153, 1129, 835, 762. Anal. Calcd for $C_{18}H_{12}FN_3O_3$: C, 64.09%; H, 3.59%; N, 12.46%. Found: C, 64.00%; H, 3.63%; N, 12.43%.

6h. White solid, mp: 58−59 °C. ^1H NMR ($CDCl_3$) δ 9.26 (1H, s), 7.94−7.92 (1H, m), 7.91 (2H, d, J = 9.2 Hz), 7.56−7.54 (1H, m), 7.47−7.41 (2H, m), 7.04 (2H, d, J = 9.2 Hz), 3.88 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.1, 167.6, 162.4, 161.6, 159.7, 133.6, 131.9, 131.7, 131.1, 130.9, 128.9, 127.0, 119.3, 114.2, 106.5, 55.4; MS *m*/*z* 139 (100), 353 (M^+); IR ν_{max} (cm^{-1}) 2929, 2855, 1645, 1615, 1474, 1257, 1144, 755. Anal.

Calcd for $C_{18}H_{12}ClN_3O_3$: C, 61.11%; H, 3.42%; N, 11.88%. Found: C, 61.19%; H, 3.45%; N, 11.82%.

6i. White solid, mp: 115−117 °C. ^{1}H NMR ($CDCl_3$) δ 8.15−8.12 (2H, m), 7.53−7.48 (3H, m), 7.04 (1H, s), 2.91−2.85 (1H, m), 2.06−1.27 (10H, m); ^{13}C NMR ($CDCl_3$) δ 169.1, 165.5, 160.8, 154.7, 131.6, 128.9, 127.6, 125.8, 106.9, 35.7, 31.9, 25.7, 25.6; MS *m*/*z* 55 (100), 295 (M^+); IR ν_{max} (cm^{-1}) 2927, 2852, 1654, 1531, 1447, 1360, 897, 745, 698. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14%; H, 5.80%; N, 14.23%. Found: C, 69.20%; H, 5.77%; N, 14.19%.

6j. White solid, mp: 112−115 °C. ^{1}H NMR ($CDCl_3$) δ 8.04 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.03 (1H, s), 2.91−2.85 (1H, m), 2.41(3H, s), 2.03−1.28 (10H, m); ^{13}C NMR ($CDCl_3$) δ 169.0, 165.3, 160.7, 154.7, 142.0, 129.6, 127.4, 122.9, 106.8, 35.6, 31.8, 25.7, 25.6, 21.5; MS *m*/*z* 55 (100), 309 (M^+); IR ν_{max} (cm^{-1}) 3114, 2933, 2851, 1654, 1614, 1531, 1479, 1451, 1412, 1350, 1123, 896, 757. Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88%; H, 6.19%; N, 13.58%. Found: C, 69.80%; H, 6.23%; N, 13.63%.

6k. Pale yellow solid, mp: 125−128 °C. ^{1}H NMR ($CDCl_3$) δ 8.04 (2H, d, J = 8.4 Hz), 7.67 (2H, d, J = 8.4 Hz), 7.05 (1H, s), 2.93−2.87 (1H, m), 2.07−1.25 (10H, m); ^{13}C NMR ($CDCl_3$) δ 169.2, 168.4, 165.7, 154.6, 132.3, 129.1, 126.4, 124.8, 107.1, 35.7, 31.9, 25.8, 25.7; MS *m*/*z* 55 (100), 373 (M^+), 375 (M + 2); IR ν_{max} (cm^{-1}) 2930, 2854, 1650, 1599, 1530, 1406, 1347, 1122, 1013, 757, 900, 837. Anal. Calcd for $C_{17}H_{16}BrN_3O_2$: C, 54.56%; H, 4.31%; N, 11.23%. Found: C, 54.43%; H, 4.40%; N, 11.16%.

6l. White solid, mp: 108−111 °C. ^{1}H NMR ($CDCl_3$) δ 8.12 (2H, d, J = 8.4 Hz), 7.51 (2H, d, J = 8.4 Hz), 7.05 (1H, s), 2.93−2.87 (1H, m), 2.07−1.25 (10H, m); ^{13}C NMR ($CDCl_3$) δ 169.2, 168.4, 165.7, 154.6, 138.0, 129.3, 128.9, 124.4, 107.0, 35.7, 31.9, 25.8, 25.7; MS *m*/*z* 55 (100), 329 (M^+); IR ν_{max} (cm^{-1}) 2931, 2853, 1650, 1602, 1530, 1470, 1448, 1409, 1349, 1092, 839, 758. Anal. Calcd for $C_{17}H_{16}ClN_3O_2$: C, 61.91%; H, 4.89%; N, 12.74%. Found: C, 61.78%; H, 4.83%; N, 12.70%.

6m. White solid, mp: 85−87 °C. ^{1}H NMR ($CDCl_3$) δ 7.99−7.96 (1H, m), 7.54−7.52 (1H, m), 7.46−7.37 (2H, m), 7.05 (1H, s), 2.89−2.83 (1H, m), 2.03−1.25 (10H, m); ^{13}C NMR ($CDCl_3$) δ 169.1, 167.8, 165.0, 154.5, 133.4, 132.1, 131.7, 130.9, 126.9, 125.1, 107.1, 35.6, 31.8, 25.7, 25.6; MS *m*/*z* 55 (100), 329 (M^+); IR ν_{max} (cm^{-1}) 3112, 2929, 2853, 1652, 1530, 1472, 1344, 1096, 1051, 755. Anal. Calcd for $C_{17}H_{16}ClN_3O_2$: C, 61.91%; H, 4.89%; N, 12.74%. Found: C, 61.83%; H, 4.98%; N, 12.68%.

6n. Pale yellow solid, mp: 160−161 °C. ^{1}H NMR ($CDCl_3$) δ 8.33−8.32 (1H, m), 8.11−8.09 (1H, m), 7.69−7.67 (1H, m), 7.42−7.38 (1H, m), 7.07 (1H, s), 2.93−2.88 (1H, m), 2.07−1.29 (10H, m); ^{13}C NMR ($CDCl_3$) δ 169.2, 168.0, 165.8, 154.6, 134.7, 130.6, 130.5, 137.8, 126.1, 123.1, 107.2, 35.7, 31.9, 25.8, 25.7; MS *m*/*z* 55 (100), 373 (M^+), 375 (M + 2); IR ν_{max} (cm^{-1}) 3105, 2929, 2853, 1652, 1530, 1445, 1344, 899, 751. Anal. Calcd for $C_{17}H_{16}BrN_3O_2$: C, 54.56%; H, 4.31%; N, 11.23%. Found: C, 54.60%; H, 4.35%; N, 11.20%.

6o. Pale yellow solid, mp: 162−163 °C. ^{1}H NMR ($CDCl_3$) δ 9.29 (1H, s), 8.08−8.06 (2H, m), 7.90 (2H, d, J = 8.8 Hz), 7.53−7.50 (5H, m); ^{13}C NMR ($CDCl_3$) δ 168.7, 168.1, 162.4, 159.1, 137.0, 131.5, 130.8, 128.9, 128.8, 127.4, 126.1, 125.1, 106.7; MS *m*/*z* 118 (100), 323 (M^+); IR ν_{max} (cm^{-1}) 2926, 2855, 1643, 1448, 1416, 1362, 1140, 1096, 827, 748, 689. Anal. Calcd for $C_{17}H_{10}ClN_3O_2$: C, 63.07%; H, 3.11%; N, 12.98%. Found: C, 62.98%; H, 3.25%; N, 12.91%.

6p. White solid, mp: 137−139 °C. ^{1}H NMR ($CDCl_3$) δ 9.27 (1H, s), 7.99 (2H, d, J = 8.0 Hz), 7.90 (2H, d, J = 8.8 Hz), 7.52 (2H, d, J = 8.8 Hz), 7.31 (2H, d, J = 8.0 Hz), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.7, 167.9, 162.4, 159.1, 142.0, 137.0, 130.8, 129.7, 128.8, 127.4, 125.1, 123.3, 106.8, 21.6; MS *m*/*z* 132 (100), 337 (M^+); IR ν_{max} (cm^{-1}) 3129, 2924, 1729, 1641, 1483, 1419, 1361, 1146, 1093, 826, 758. Anal. Calcd for $C_{18}H_{12}ClN_3O_2$: C, 64.01%; H, 3.58%; N, 12.44%. Found: C, 64.09%; H, 3.65%; N, 12.47%.

6q. Pale yellow solid, mp: 178−179 °C. ^{1}H NMR ($CDCl_3$) δ 9.28 (1H, s), 7.94 (2H, d, J = 8.4 Hz), 7.87 (2H, d, J = 8.4 Hz), 7.65 (2H, d, J = 8.0 Hz), 7.52 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 168.3, 168.0, 162.5, 159.1, 137.0, 132.3, 130.8, 128.9, 128.8, 126.2, 125.02, 124.99, 106.6; MS *m*/*z* 177 (100), 401 (M^+), 403 (M + 2); IR ν_{max} (cm^{-1}) 2926, 1643, 1600, 1471, 1409, 1355, 1139, 1095, 1014, 828, 759. Anal. Calcd for $C_{17}H_9BrClN_3O_2$: C, 50.71%; H, 2.25%; N, 10.44%. Found: C, 50.59%; H, 2.38%; N, 10.46%.

6r. White solid, mp: 163−165 °C. ^{1}H NMR ($CDCl_3$) δ 9.29 (1H, s), 8.02 (2H, d, J = 8.8 Hz), 7.88 (2H, d, J = 8.8 Hz), 7.53 (2H, d, J = 8.8 Hz), 7.50 (2H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 168.3, 168.0, 162.5, 159.1, 137.8, 137.1, 130.8, 129.3, 128.9, 128.8, 125.0, 124.6, 106.6; MS *m*/*z* 177 (100), 357 (M^+); IR ν_{max} (cm^{-1}) 2925, 1729, 1642, 1603, 1473, 1412, 1141, 1096, 828, 736. Anal. Calcd for $C_{17}H_9Cl_2N_3O_2$: C, 57.01%; H, 2.53%; N, 11.73%. Found: C, 56.95%; H, 2.58%; N, 11.66%.

6s. White solid, mp: 97−99 °C. ^{1}H NMR ($CDCl_3$) δ 8.20−8.18 (2H, m), 7.86−7.83 (1H, m), 7.68 (1H, s), 7.56−7.52 (4H, m), 7.49−7.42 (2H, m); ^{13}C NMR ($CDCl_3$) δ 169.3, 165.3, 161.8, 155.2, 133.0, 131.8, 131.7, 131.1, 130.6, 129.0, 127.7, 127.4, 126.7, 125.8, 109.5; MS *m*/*z* 178 (100), 323 (M^+); IR ν_{max} (cm^{-1}) 2925, 1652, 1532, 1448, 1357, 1137, 1075, 741, 694. Anal. Calcd for $C_{17}H_{10}ClN_3O_2$: C, 63.07%; H, 3.11%; N, 12.98%. Found: C, 63.10%; H, 3.15%; N, 12.92%.

6t. White solid, mp: 151−153 °C. ^{1}H NMR ($CDCl_3$) δ 8.09 (2H, d, J = 8.0 Hz) 7.86−7.83 (1H, m), 7.67 (1H, s), 7.56−7.54 (1H, m), 7.49−7.40 (2H, m), 7.35 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 169.3, 165.1, 161.8, 155.3, 142.3, 133.0, 131.7, 131.1, 130.6, 129.7, 127.6, 127.4, 126.7, 123.0, 109.4, 21.6; MS *m*/*z* 178 (100), 337 (M^+); IR ν_{max} (cm^{-1}) 3115, 2925, 1651, 1614, 1529, 1492, 1418, 1355, 1138, 1041, 905, 769, 728. Anal. Calcd for $C_{18}H_{12}ClN_3O_2$: C, 64.01%; H, 3.58%; N, 12.44%. Found: C, 63.95%; H, 3.65%; N, 12.39%.

6u. White solid, mp: 136−138 °C. ^{1}H NMR ($CDCl_3$) δ 8.22−8.18 (2H, m), 7.86−7.83 (1H, m), 7.68 (1H, s), 7.57−7.54 (1H, m), 7.47−7.42 (2H, m), 7.24−7.20 (2H, m); ^{13}C NMR ($CDCl_3$) δ 168.5, 165.4, 164.9 (J = 251.3 Hz), 161.8, 155.1, 133.0, 131.7, 131.1, 130.6, 129.9 (J = 9.7 Hz), 127.4, 126.7, 122.1 (J = 4.1 Hz), 116.3 (J = 21.7 Hz), 109.6; MS *m*/*z* 178 (100), 341 (M^+); IR ν_{max} (cm^{-1}) 1068, 1530, 1493, 1422, 1351, 1235, 1159, 842, 758. Anal. Calcd for $C_{17}H_9$-

$ClFN_3O_2$: C, 59.75%; H, 2.65%; N, 12.30%. Found: C, 59.79%; H, 2.62%; N, 12.34%.

6v. Pale yellow solid, mp: 160−162 °C. ^{1}H NMR ($CDCl_3$) δ 9.35 (1H, s), 8.42 (2H, d, J = 8.8 Hz), 8.20 (2H, d, J = 8.8 Hz), 7.95 (2H, d, J = 8.0 Hz), 7.32 (2H, d, J = 8.0 Hz), 2.43 (3H,s); ^{13}C NMR ($CDCl_3$) δ 168.8, 167.5, 162.7, 158.4, 149.2, 142.2, 133.0, 130.7, 129.7, 127.4, 123.6, 123.1, 107.0, 21.6; MS *m*/*z* 132 (100), 348 (M^+); IR ν_{max} (cm^{-1}) 3119, 2923, 2854, 1647, 1521, 1420, 1351, 1138, 853, 756. Anal. Calcd for $C_{18}H_{12}N_4O_4$: C, 62.07%; H, 3.47%; N, 16.09%. Found: C, 62.00%; H, 3.53%; N, 16.16%.

6w. Pale yellow solid, mp: 104−106 °C. ^{1}H NMR ($CDCl_3$) δ 8.19−8.16 (2H, m), 7.58−7.53 (4H, m), 4.52 (2H, q, J = 7.2 Hz), 1.47 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 169.4, 164.6, 158.6, 157.2, 157.0, 131.9, 129.1, 127.7, 125.6, 108.6, 62.9, 14.1; MS *m*/*z* 285 (M^+, 100); IR ν_{max} (cm^{-1}) 3137, 2926, 2855, 1728, 1446, 1354, 1272, 1182, 1115, 1013, 933, 745, 697. Anal. Calcd for $C_{14}H_{11}N_3O_4$: C, 58.95%; H, 3.89%; N, 14.73%. Found: C, 58.91%; H, 3.93%; N, 14.77%.

Typical Procedure for the Preparation of the Substituted 4-(1,2,4-Oxadiazol-5-yl)-1*H*-1,2,3-triazole 9 (Products 9a−o). Under a positive pressure of nitrogen, to a suspension of the swollen resin 7 (0.6 g) in DMSO (10 mL) was added NaN_3 (2.0 mmol), ArI (4.0 mmol), proline (0.25 mmol), CuI (0.25 mmol), and Et_3N (0.25 mmol). The mixture was stirred at 65 °C for 15 h. The resin **8** was collected by filtration and washed with DMF (10 mL × 3), DMF/0.1 N HCl (3:1) (10 mL × 2), H_2O (10 mL × 3), and THF (10 mL × 3).

The washed resin **8** was suspended in THF (15 mL), 30% (aq) H_2O_2 (0.5 mL) was added, and the mixture was stirred for 30 min at 0 °C, followed by 40 min at room temperature. The mixture was filtered, and the resin was washed with CH_2Cl_2 (15 mL × 2). The filtrate was washed with H_2O (30 mL × 2), dried over $MgSO_4$, and evaporated to dryness under vacuum to obtain the crude products **9**. Further purification was via flash chromatography with *n*-hexanes/EtOAc (6:1 v/v) as the eluent for ^{13}C NMR and microanalysis.

9a. White solid, mp: 177−180 °C. ^{1}H NMR ($CDCl_3$) δ 8.75 (1H, s), 8.21−8.18 (2H, m), 7.85−7.82 (2H, m), 7.62−7.51 (6H, m); ^{13}C NMR ($CDCl_3$) δ 168.9, 168.5, 136.1, 135.0, 131.4, 130.0, 129.8, 128.9, 127.6, 126.3, 123.6, 120.8; MS *m*/*z* 77 (100), 289 (M^+); IR ν_{max} (cm^{-1}) 3139, 2923, 1642, 1492, 1446, 1386, 1344, 1106, 1042, 764, 749, 688. Anal. Calcd for $C_{16}H_{11}N_5O$: C, 66.43%; H, 3.83%; N, 24.21%. Found: C, 66.51%; H, 3.89%; N, 24.12%.

9b. White solid, mp: 207−209 °C. ^{1}H NMR ($CDCl_3$) δ 8.74 (1H, s), 8.09 (2H, d, J = 8.4 Hz), 7.84 (2H, d, J = 7.6 Hz), 7.62−7.54 (3H, m), 7.33 (2H, d, J = 7.6 Hz), 2.43 (3H, m); ^{13}C NMR ($CDCl_3$) δ 168.9, 168.4, 141.8, 136.2, 135.1, 130.0, 129.8, 129.6, 127.5, 123.6, 123.5, 120.8, 21.6; MS *m*/*z* 149 (100), 303 (M^+); IR ν_{max} (cm^{-1}) 2925, 2855, 1642, 1492, 1462, 1413, 1337, 1041, 760. Anal. Calcd for $C_{17}H_{13}N_5O$: C, 67.32%; H, 4.32%; N, 23.09%. Found: C, 67.21%; H, 4.40%; N, 23.05%.

9c. Pale yellow solid, mp: 228−229 °C. ^{1}H NMR ($CDCl_3$) δ 8.74 (1H, s), 8.08 (2H, d, J = 8.4 Hz), 7.85−7.82 (2H, m), 7.68 (2H, d, J = 8.4 Hz), 7.63−7.55 (3H, m); ^{13}C NMR ($CDCl_3$) δ 168.8, 168.2, 136.2, 134.9, 132.2, 130.1, 129.9, 129.1, 126.1, 125.4, 123.7, 120.9; MS *m*/*z* 144 (100), 367 (M^+), 369 (M + 2); IR ν_{max} (cm^{-1}) 3134, 1639, 1598, 1484, 1405, 1332, 1152, 1042, 832, 756. Anal. Calcd for $C_{16}H_{10}BrN_5O$: C, 52.19%; H, 2.74%; N, 19.02%. Found: C, 52.13%; H, 2.78%; N, 19.05%.

9d. White solid, mp: 227−228 °C. ^{1}H NMR ($CDCl_3$) δ 8.74 (1H, s), 8.16 (2H, d, J = 8.4 Hz), 7.85−7.83 (2H, m), 7.63−7.55 (3H, m), 7.52 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 168.8, 168.2, 137.7, 136.2, 134.9, 130.1, 129.9, 129.3, 129.0, 124.9, 123.7, 120.9; MS *m*/*z* 144 (100), 323 (M^+); IR ν_{max} (cm^{-1}) 3135, 2924, 1639, 1600, 1486, 1407, 1334, 1097, 1042, 759. Anal. Calcd for $C_{16}H_{10}ClN_5O$: C, 59.36%; H, 3.11%; N, 21.63%. Found: C, 59.29%; H, 3.19%; N, 21.60%.

9e. White solid, mp: 205−206 °C. ^{1}H NMR ($CDCl_3$) δ 8.74 (1H, s), 8.21−8.17 (2H, m), 7.83−7.81 (2H, m), 7.61−7.57 (2H, m), 7.55−7.51 (1H, m), 7.22−7.17 (2H, m); ^{13}C NMR ($CDCl_3$) δ 168.7, 168.1, 164.7 (J = 250.3 Hz), 136.1, 134.9, 130.1, 129.8 (J = 8.2 Hz), 129.2, 123.6, 122.6 (J = 2.8 Hz), 120.9, 116.1 (J = 21.9 Hz); MS *m*/*z* 144 (100), 307 (M^+); IR ν_{max} (cm^{-1}) 3118, 2926, 1641, 1606, 1493, 1416, 1335, 1231, 1155, 1039, 760. Anal. Calcd for $C_{16}H_{10}FN_5O$: C, 62.54%; H, 3.28%; N, 22.79%. Found: C, 62.59%; H, 3.31%; N, 22.73%.

9f. White solid, mp: 172−174 °C. ^{1}H NMR ($CDCl_3$) δ 8.76 (1H, s), 8.05−8.02 (1H, m), 7.83−7.81 (2H, m), 7.60−7.39 (6H, m); ^{13}C NMR ($CDCl_3$) δ 168.1, 167.7, 136.1, 134.8, 133.5, 131.9, 130.9, 130.0, 129.8, 126.9, 125.7, 123.8, 120.8; MS *m*/*z* 144 (100), 323 (M^+); IR ν_{max} (cm^{-1}) 3144, 3060, 1638, 1598, 1481, 1328, 1261, 1042, 761. Anal. Calcd for $C_{16}H_{10}ClN_5O$: C, 59.36%; H, 3.11%; N, 21.63%. Found: C, 59.22%; H, 3.21%; N, 21.65%.

9g. Pale yellow solid, mp: 141−143 °C. ^{1}H NMR ($CDCl_3$) δ 8.75 (1H, s), 8.38−8.37 (1H, m), 8.15−8.12 (1H, m), 7.85−7.83 (2H, m), 7.68−7.55 (4H, m), 7.42−7.38 (1H, m); ^{13}C NMR ($CDCl_3$) δ 168.9, 167.8, 136.2, 134.9, 134.4, 130.7, 130.5, 130.1, 129.9, 128.3, 126.1, 123.7, 123.0, 120.9; MS *m*/*z* 77 (100), 367 (M^+), 369 (M + 2); IR ν_{max} (cm^{-1}) 3137, 2925, 2853, 1643, 1486, 1339, 1262, 1042, 759, 685. Anal. Calcd for $C_{16}H_{10}BrN_5O$: C, 52.19%; H, 2.74%; N, 19.02%. Found: C, 52.27%; H, 2.72%; N, 18.99%.

9h. White solid, mp: 187−189 °C. ^{1}H NMR ($CDCl_3$) δ 8.70 (1H, s), 8.22−8.19 (2H, m), 7.71 (2H, d, J = 8.0 Hz), 7.54−7.52 (3H, m), 7.40 (2H, d, J = 8.0 Hz), 2.47 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.9, 168.6, 140.1, 134.9, 133.9, 131.4, 130.5, 128.9, 127.6, 126.6, 123.5, 120.8, 21.1; MS *m*/*z* 158 (100), 303 (M^+); IR ν_{max} (cm^{-1}) 3299, 3134, 2928, 2854, 1645, 1521, 1445, 1343, 1042, 828, 748, 691. Anal. Calcd for $C_{17}H_{13}N_5O$: C, 67.32%; H, 4.32%; N, 23.09%. Found: C, 67.37%; H, 4.34%; N, 23.04%.

9i. White solid, mp: 202−205 °C. ^{1}H NMR ($CDCl_3$) δ 8.68 (1H, s), 8.10 (2H, d, J = 8.0 Hz), 7.71 (2H, d, J = 8.0 Hz), 7.40 (2H, d, J = 8.0 Hz), 7.34 (2H, d, J = 8.0 Hz), 2.47 (3H, s), 2.44 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.9, 168.5, 141.8, 140.1, 135.0, 134.0, 130.6, 129.6, 127.6, 123.6, 123.5, 120.8, 21.6, 21.2; MS *m*/*z* 158 (100), 317 (M^+); IR ν_{max} (cm^{-1}) 3137, 2924, 2853, 1640, 1521, 1048, 1336, 1041,

827, 757. Anal. Calcd for $C_{18}H_{15}N_5O$: C, 68.13%; H, 4.76%; N, 22.07%. Found: C, 68.01%; H, 4.82%; N, 22.14%.

9j. White solid, mp: 220−222 °C. ^{1}H NMR ($CDCl_3$) δ 8.68 (1H, s), 8.09 (2H, d, J = 8.4 Hz), 7.71 (2H, d, J = 8.4 Hz), 7.68 (2H, d, J = 8.0 Hz), 7.40 (2H, d, J = 8.0 Hz), 2.47 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.9, 168.2, 140.2, 134.7, 133.9, 132.2, 130.6, 129.2, 126.1, 125.4, 123.6, 120.8, 21.2; MS m/z 43 (100), 381 (M^+), 383 (M + 2); IR ν_{max} (cm^{-1}) 3135, 2923, 1637, 1602, 1405, 1100, 1043, 832, 758. Anal. Calcd for $C_{17}H_{12}BrN_5O$: C, 53.42%; H, 3.16%; N, 18.32%. Found: C, 53.46%; H, 3.18%; N, 18.29%.

9k. Pale yellow solid, mp: 140−141 °C. ^{1}H NMR ($CDCl_3$) δ 8.54 (1H, s), 8.15−8.14 (1H, m), 7.95−7.93 (1H, m), 7.66−7.64 (1H, m), 7.47 (2H, d, J = 8.4 Hz), 7.40−7.34 (3H, m), 2.51 (3H, s); ^{13}C NMR ($CDCl_3$) δ 167.8, 166.1, 141.0, 137.3, 134.7, 133.3, 130.6, 130.5, 129.8, 127.8, 126.0, 125.7, 124.0, 123.0, 21.3; MS m/z 158 (100), 381 (M^+), 383 (M + 2); IR ν_{max} (cm^{-1}) 2925, 1633, 1516, 1402, 1355, 1169, 1122, 1073, 820, 751. Anal. Calcd for $C_{17}H_{12}BrN_5O$: C, 53.42%; H, 3.16%; N, 18.32%. Found: C, 53.35%; H, 3.27%; N, 18.38%.

9l. White solid, mp: 146−148 °C. ^{1}H NMR ($CDCl_3$) δ 8.51 (1H, s), 8.22−8.19 (2H, m), 7.54−7.48 (4H, m), 7.45−7.41 (3H, m), 2.29 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.9, 168.7, 135.5, 134.4, 133.7, 131.7, 131.4, 130.7, 128.9, 127.6, 127.1, 127.0, 126.4, 125.9, 17.8; MS m/z 129 (100), 303 (M^+); IR ν_{max} (cm^{-1}) 3135, 2929, 1642, 1488, 1447, 1418, 1383, 1341, 1042, 768, 694. Anal. Calcd for $C_{17}H_{13}N_5O$: C, 67.32%; H, 4.32%; N, 23.09%. Found: C, 67.22%; H, 4.41%; N, 23.01%.

9m. White solid, mp: 169−170 °C. ^{1}H NMR ($CDCl_3$) δ 8.49 (1H, s), 8.09 (2H, d, J = 8.0 Hz), 7.47−7.39 (4H, m), 7.32 (2H, d, J = 8.0 Hz), 2.43 (3H, s), 2.28 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.9, 168.5, 141.8, 135.5, 134.4, 133.7, 131.7, 130.6, 129.6, 127.5, 127.1, 127.0, 125.9, 123.5, 21.6, 17.8; MS m/z 91 (100), 317 (M^+); IR ν_{max} (cm^{-1}) 3111, 2925, 1640, 1494, 1413, 1336, 1104, 1041, 763. Anal. Calcd for $C_{18}H_{15}N_5O$: C, 68.13%; H, 4.76%; N, 22.07%. Found: C, 68.03%; H, 4.83%; N, 22.02%.

9n. Pale yellow solid, mp: 149−151 °C. ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, s), 8.07 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.50−7.39 (4H, m), 2.28 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.9, 168.2, 135.4, 134.2, 133.7, 132.2, 131.8, 130.7, 129.1, 127.2, 127.1, 126.0, 125.9, 125.3, 17.8; MS m/z 157 (100), 381 (M^+), 383 (M + 2); IR ν_{max} (cm^{-1}) 3130, 2928, 1643, 1596, 1470, 1407, 1332, 1042, 1009, 844, 761. Anal. Calcd for $C_{17}H_{12}BrN_5O$: C, 53.42%; H, 3.16%; N, 18.32%. Found: C, 53.40%; H, 3.19%; N, 18.36%.

9o. White solid, mp: 102−104 °C. ^{1}H NMR ($CDCl_3$) δ 8.59 (1H, s), 8.81−7.78 (1H, m), 7.54−7.50 (2H, m), 7.43−7.33 (5H, m), 2.07 (3H, s); ^{13}C NMR ($CDCl_3$) δ 167.7, 165.0, 136.6, 135.4, 135.2, 133.6, 132.1, 131.6, 131.2, 131.1, 131.0, 127.2, 126.9, 126.8, 125.0, 124.8, 17.2; MS m/z 129 (100), 337 (M^+); IR ν_{max} (cm^{-1}) 2923, 2853, 1621, 1523, 1497, 1463, 1348, 1173, 1121, 1046, 752. Anal. Calcd for $C_{17}H_{12}ClN_5O$: C, 60.45%; H, 3.58%; N, 20.73%. Found: C, 60.50%; H, 3.60%; N, 20.69%.

Typical Procedure for the Preparation of the Substituted 5-(Bicyclo[2.2.1]hepta-2,5-dien-2-yl)-1,2,4-oxadiazole 11 (Products 11a−h). Under a positive pressure of nitrogen, to a suspension of the swollen resin **7** (0.6 g) in CH_2Cl_2 (15 mL) was added ZnI_2 (0.6 mmol). The mixture was stirred for 10 min, and cyclopentadiene (2.5 mmol) was added. The reaction was stirred for 12 h at room temperature. Resin **10** was collected by filtration and washed with saturated aqueous solution of $NaHCO_3$ (20 mL × 2), THF (10 mL × 2), H_2O (10 mL × 2), THF/H_2O (2:1) (10 mL × 2), THF (10 mL × 2), CH_2Cl_2 (10 mL × 2), and THF (10 mL × 2).

The washed resin **10** was suspended in THF (15 mL), 30% (aq) H_2O_2 (0.5 mL) was added, and the mixture was stirred for 20 min at 0 °C followed by 1.0 h at room temperature. The mixture was filtered, and the resin was washed with CH_2Cl_2 (15 mL × 2). The filtrate was washed with H_2O (30 mL × 2), dried over $MgSO_4$, and evaporated to dryness under vacuum to obtain the crude products **11**. Further purification was via flash chromatography with *n*-hexanes/EtOAc (15:1 v/v) as the eluent for ^{13}C NMR and microanalyses.

11a. Oil. ^{1}H NMR ($CDCl_3$) δ 8.12−8.10 (2H, m), 7.86 (1H, d, J = 3.2 Hz), 7.50−7.48 (3H, m), 7.00−6.98 (1H, m), 6.83−6.81 (1H, m), 4.25−4.24 (1H, m), 3.87−3.86 (1H, m), 2.29−2.22 (2H, m); ^{13}C NMR ($CDCl_3$) δ 173.4, 168.7, 153.4, 143.0, 142.3, 141.9, 131.0, 128.7, 127.4, 127.1, 74.0, 52.0, 51.3; MS m/z 119 (100), 236 (M^+); IR ν_{max} (cm^{-1}) 2931, 1711, 1445, 1360, 1119, 1072, 748, 695. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25%; H, 5.12%; N, 11.86%. Found: C, 76.15%; H, 5.21%; N, 11.81%.

11b. Oil. ^{1}H NMR ($CDCl_3$) δ 8.01 (2H, d, J = 8.0 Hz), 7.85 (1H, d, J = 3.2 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.00−6.98 (1H, m), 6.83−6.81 (1H, m), 4.24−4.23 (1H, m), 3.87−3.86 (1H, m), 2.42 (3H, s), 2.29−2.22 (2H, m); ^{13}C NMR ($CDCl_3$) δ 173.3, 168.6, 153.2, 143.0, 142.3, 141.9, 141.3, 129.5, 127.3, 124.3, 74.0, 52.0, 51.3, 21.4; MS m/z 195 (100), 250 (M^+); IR ν_{max} (cm^{-1}) 2928, 2855, 1713, 1669, 1617, 1414, 1363, 1114, 829, 760. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78%; H, 5.64%; N, 11.19%. Found: C, 76.61%; H, 5.75%; N, 11.11%.

11c. Oil. ^{1}H NMR ($CDCl_3$) δ 8.06 (2H, d, J = 8.8 Hz), 7.85 (1H, d, J = 3.2 Hz), 7.00−6.98 (3H, m), 6.83−6.81 (1H, m), 4.23 (1H, s), 3.87 (4H, s), 2.29−2.22 (2H, m); ^{13}C NMR ($CDCl_3$) δ 173.2, 168.3, 161.8, 153.1, 143.0, 142.3, 141.9, 129.0, 119.6, 114.2, 74.0, 55.3, 52.0, 51.3; MS m/z 266 (M^+, 100); IR ν_{max} (cm^{-1}) 2938, 1613, 1515, 1473, 1422, 1364, 1301, 1255, 1175, 1030, 840, 763. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16%; H, 5.30%; N, 10.52%. Found: C, 72.01%; H, 5.40%; N, 10.58%.

11d. Low-point solid. ^{1}H NMR ($CDCl_3$) δ 8.00 (2H, d, J = 8.4 Hz), 7.87 (1H, d, J = 3.2 Hz), 7.63 (2H, d, J = 8.4 Hz), 7.00−6.98 (1H, m), 6.83−6.81 (1H, m), 4.23−4.22 (1H, m), 3.88−3.87 (1H, m), 2.29−2.23 (2H, m); ^{13}C NMR ($CDCl_3$) δ 173.6, 167.9, 153.8, 143.0, 142.3, 141.7, 132.0, 128.9, 126.0, 125.5, 74.1, 52.0, 51.3; MS m/z 56 (100), 314 (M^+), 316 (M + 2); IR ν_{max} (cm^{-1}) 2929, 1701, 1626, 1600, 1466, 1070, 1012, 837, 759. Anal. Calcd for $C_{15}H_{11}BrN_2O$: C, 57.16%; H, 3.52%; N, 8.89%. Found: C, 57.27%; H, 3.61%; N, 8.80%.

11e. Low-point solid. ^{1}H NMR ($CDCl_3$) δ 8.06−8.03 (2H, m), 7.86 (1H, d, J = 3.2 Hz), 7.47−7.43 (2H, m), 7.00−

6.98 (1H, m), 6.82−6.80 (1H, m), 4.23−4.22 (1H, m), 3.87−3.86 (1H, m), 2.28−2.22 (2H, m); ^{13}C NMR ($CDCl_3$) δ 173.6, 167.8, 153.7, 142.9, 142.3, 141.7, 137.1, 129.1, 128.7, 125.6, 74.0, 52.0, 51.3; MS *m*/*z* 66 (100), 270 (M^+); IR ν_{max} (cm^{-1}) 2938, 1721, 1600, 1468, 1408, 1353, 1092, 1016, 840, 760, 509. Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55%; H, 4.10%; N, 10.35%. Found: C, 66.44%; H, 4.21%; N, 10.30%.

11f. Oil. ^{1}H NMR ($CDCl_3$) δ 8.13−8.09 (2H, m), 7.86 (1H, d, J = 3.2 Hz), 7.19−7.14 (2H, m), 7.00−6.98 (1H, m), 6.83−6.81 (1H, m), 4.23−4.22 (1H, m), 3.88−3.87 (1H, m), 2.29−2.22 (2H, m); ^{13}C NMR ($CDCl_3$) δ 173.5, 167.8, 164.5 (J = 249.5 Hz), 153.6, 142.9, 142.4, 141.8, 129.6 (J = 9.5 Hz), 123.3 (J = 4.3 Hz), 115.9 (J = 22.1 Hz), 74.1, 52.0, 51.3; MS *m*/*z* 66 (100), 254 (M^+); IR ν_{max} (cm^{-1}) 2930, 1720, 1608, 1481, 1417, 1353, 1228, 1157, 846, 763, 620. Anal. Calcd for $C_{15}H_{11}FN_2O$: C, 70.86%; H, 4.36%; N, 11.02%. Found: C, 70.76%; H, 4.43%; N, 11.08%.

11g. Oil. ^{1}H NMR ($CDCl_3$) δ 7.93−7.88 (2H, m), 7.54−7.52 (1H, m), 7.45−7.36 (2H, m), 7.00−6.98 (1H, m), 6.83−6.81 (1H, m), 4.23 (1H, s), 3.88−3.87 (1H, m), 2.30−2.22 (2H, m); ^{13}C NMR ($CDCl_3$) δ 173.0, 167.4, 153.8, 142.9, 142.3, 141.6, 133.4, 131.6, 131.5, 130.8, 126.8, 126.4, 74.0, 52.0, 51.2; MS *m*/*z* 66 (100), 270 (M^+); IR ν_{max} (cm^{-1}) 2937, 1705, 1626, 1592, 1467, 1344, 1056, 754. Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55%; H, 4.10%; N, 10.35%. Found: C, 66.65%; H,4.21%; N, 10.21%.

11h. Oil. ^{1}H NMR ($CDCl_3$) δ 8.28−8.27 (1H, m), 8.06−8.03 (1H, m), 7.88 (1H, d, J = 3.2 Hz), 7.64−7.61 (1H, m), 7.37−7.33 (1H, m), 7.00−6.98 (1H, m), 6.83−6.81 (1H, m), 4.23 (1H, s), 3.88−3.87 (1H, m), 2.29−2.23 (2H, m); ^{13}C NMR ($CDCl_3$) δ 173.8, 167.5, 153.9, 143.0, 142.3, 141.7, 134.0, 130.4, 130.3, 129.1, 126.0, 122.9, 74.1, 52.1, 51.3; MS *m*/*z* 66 (100), 314 (M^+), 316 (M + 2); IR ν_{max} (cm^{-1}) 2928, 1718, 1625, 1559, 1521, 1436, 1401, 1340, 1072, 758, 744. Anal. Calcd for $C_{15}H_{11}BrN_2O$: C, 57.16%; H, 3.52%; N, 8.89%. Found: C, 57.03%; H, 3.63%; N, 8.83%.

Typical Procedure for the Preparation of the Substituted 5-(4-Methylcyclohexa-1,3-dienyl)-1,2,4-oxadiazole 13 (Products 13a−h). Under a positive pressure of nitrogen, to a suspension of the swollen resin **11** (0.6 g) in CH_2Cl_2 (15 mL) was added ZnI_2 (0.6 mmol). The mixture was stirred for 10 min, and isoprene (2.5 mmol) was added. The reaction was stirred for 48 h at room temperature. Resin **12** was collected by filtration and washed with saturated aqueous solution of $NaHCO_3$ (20 mL × 2), THF (10 mL × 2), H_2O (10 mL × 2), THF/H_2O (2:1) (10 mL × 2), THF (10 mL × 2), CH_2Cl_2 (10 mL × 2), and THF (10 mL × 2).

The washed resin **12** was suspended in THF (15 mL), 30% (aq) H_2O_2 (0.5 mL) was added, and the mixture was stirred for 20 min at °C, followed by 40 min at room temperature. The mixture was filtered, and the resin was washed with CH_2Cl_2 (15 mL × 2). The filtrate was washed with H_2O (30 mL × 2), dried over $MgSO_4$, and evaporated to dryness under vacuum to obtain the crude products **13**. Further purification was via flash chromatography with *n*-hexanes/EtOAc (15:1 v/v) as the eluent for ^{13}C NMR and microanalyses.

13a. Low-point solid. ^{1}H NMR ($CDCl_3$) δ 8.12−8.09 (2H, m), 7.48−7.45 (3H, m), 7.16 (1H, d, J = 5.6 Hz), 5.93 (1H, d, J = 5.6 Hz), 2.79 (2H, t, J = 10.0 Hz), 2.33 (2H, t, J = 10.0 Hz), 1.91 (3H, s); ^{13}C NMR ($CDCl_3$) δ 176.2, 168.4, 144.4, 132.4, 130.8, 128.7, 127.3, 127.2, 119.3, 117.5, 28.3, 23.6, 22.1; MS *m*/*z* 119 (100), 238 (M^+); IR ν_{max} (cm^{-1}) 2928, 1586, 1548, 1443, 1358, 1128, 832, 735, 694. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61%; H, 5.92%; N, 11.76%. Found: C, 75.65%; H, 5.95%; N, 11.69%.

13b. Pale yellow solid, mp: 82−84 °C. ^{1}H NMR ($CDCl_3$) δ 8.00 (2H, d, J = 8.4 Hz), 7.28 (2H, d, J = 8.4 Hz), 7.15 (1H, d, J = 5.6 Hz), 5.93 (1H, d, J = 5.6 Hz), 2.79 (2H, t, J = 10.0 Hz), 2.41 (3H, s), 2.33 (2H, t, J = 10.0 Hz), 1.92 (3H, s); ^{13}C NMR ($CDCl_3$) δ 176.1, 168.5, 144.3, 141.1, 132.3, 129.4, 127.3, 124.4, 119.3, 117.7, 28.3, 23.6, 22.2, 21.5; MS *m*/*z* 252 (M^+, 100); IR ν_{max} (cm^{-1}) 2928, 2855, 1714, 1669, 1587, 1538, 1412, 1286, 1181, 830, 757. Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76. 16%; H, 6.39%; N, 11.10%. Found: C, 76.12%; H, 6.44%; N, 11.07%.

13c. Pale yellow solid, mp: 77−79 °C. ^{1}H NMR ($CDCl_3$) δ 8.03 (2H, d, J = 8.8 Hz), 7.09 (1H, d, J = 5.6 Hz), 6.95 (2H, d, J = 8.8 Hz), 5.87 (1H, d, J = 5.6 Hz), 3.80 (3H, s), 2.74 (2H, t, J = 10.0 Hz), 2.28 (2H, t, J = 10.0 Hz), 1.86 (3H, s); ^{13}C NMR ($CDCl_3$) δ 175.7, 167.9, 161.5, 143.9, 131.9, 128.7, 119.6, 119.1, 117.4, 113.9, 55.0, 28.1, 23.4, 22.0; MS *m*/*z* 268 (M^+, 100); IR ν_{max} (cm^{-1}) 2932, 2835, 1613, 1578, 1548, 1476, 1422, 1349, 1304, 1254, 1172, 1029, 844, 797, 640. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62%; H, 6.01%; N, 10.44%. Found: C, 71.68%; H, 5.97%; N, 10.41%.

13d. Pale yellow solid, mp: 90−92 °C. ^{1}H NMR ($CDCl_3$) δ 7.98 (2H, d, J = 8.4 Hz), 7.62 (2H, d, J = 8.4 Hz), 7.16 (1H, d, J = 5.6 Hz), 5.94 (1H, d, J = 5.6 Hz), 2.78 (2H, t, J = 10.0 Hz), 2.34 (2H, t, J = 10.0 Hz), 1.93 (3H, s); ^{13}C NMR ($CDCl_3$) δ 176.5, 167.8, 144.7, 132.7, 132.0, 128.9, 126.2, 125.4, 119.3, 117.4, 28.4, 23.7, 22.1; MS *m*/*z* 91 (100), 316 (M^+), 318 (M + 2); IR ν_{max} (cm^{-1}) 2925, 1585, 1542, 1466, 1406, 1352, 1071, 1013, 836, 753. Anal. Calcd for $C_{15}H_{13}BrN_2O$: C, 56.80%; H, 4.13%; N, 8.83%. Found: C, 56.87%; H, 4.09%; N, 8.85%.

13e. Pale yellow solid, mp: 89−91 °C. ^{1}H NMR ($CDCl_3$) δ 8.05 (2H, d, J = 8.4 Hz), 7.46 (2H, d, J = 8.4 Hz), 7.16 (1H, d, J = 5.6 Hz), 5.94 (1H, d, J = 5.6 Hz), 2.78 (2H, t, J = 10.0 Hz), 2.34 (2H, t, J = 10.0 Hz), 1.93 (3H, s); ^{13}C NMR ($CDCl_3$) δ 176.5, 167.7, 144.7, 137.0, 132.7, 129.0, 128.7, 125.8, 119.3, 117.7, 28.4, 23.7, 22.1; MS *m*/*z* 91 (100), 272 (M^+); IR ν_{max} (cm^{-1}) 2924, 1588, 1543, 1409, 1354, 1092, 837, 752, 507. Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06%; H, 4.80%; N, 10.27%. Found: C, 65.98%; H, 4.88%; N, 10.24%.

13f. Pale yellow solid, mp: 86−88 °C. ^{1}H NMR ($CDCl_3$) δ 8.12−8.08 (2H, m), 7.19−7.13 (3H, m), 5.94−5.92 (1H, m), 2.78 (2H, t, J = 10.0 Hz), 2.34 (2H, t, J = 10.0 Hz), 1.93 (3H, s); ^{13}C NMR ($CDCl_3$) δ 176.4, 167.7, 164.4 (J = 249.6 Hz), 144.7, 132.6, 129.5 (J = 8.6 Hz), 123.5 (J = 2.8 Hz), 119.3, 117.4, 115.9 (J = 21.8 Hz), 28.4, 23.7, 22.1; MS *m*/*z* 91 (100), 256 (M^+); IR ν_{max} (cm^{-1}) 2924, 1606, 1586, 1551, 1477, 1418, 1352, 1220, 1159, 845, 756, 637. Anal. Calcd for $C_{15}H_{13}FN_2O$: C, 70.30%; H, 5.11%; N, 10.93%. Found: C, 70.24%; H, 5.21%; N, 10.90%.

13g. Low-point solid. ^{1}H NMR ($CDCl_3$) δ 7.93−7.91 (1H, m), 7.54−7.52 (1H, m), 7.42−7.37 (2H, m), 7.18 (1H, d, J = 5.6 Hz), 5.94 (1H, d, J = 5.6 Hz), 2.79 (2H, t, J = 10.0 Hz), 2.34 (2H, t, J = 10.0 Hz), 1.93 (3H, s); ^{13}C NMR ($CDCl_3$) δ 175.9, 167.3, 144.7, 133.5, 132.8, 131.7, 131.4, 130.8, 126.8, 126.7, 119.3, 117.4, 28.4, 23.7, 22.2; MS *m*/*z* 91 (100), 272 (M^+); IR ν_{max} (cm^{-1}) 2925, 1584, 1544, 1467, 1428, 1343, 1045, 832, 750, 656. Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06%; H, 4.80%; N, 10.27%. Found: C, 66.10%; H, 4.83%; N, 10.23%.

13h. Pale yellow solid, mp: 69−70 °C. ^{1}H NMR ($CDCl_3$) δ 8.26−8.25 (1H, m), 8.04−8.02 (1H, m), 7.62−7.60 (1H, m), 7.34−7.32 (1H, m), 7.16 (1H, d, J = 6.0 Hz), 5.93 (1H, d, J = 6.0 Hz), 2.78 (2H, t, J = 10.0 Hz), 2.34 (2H, t, J = 10.0 Hz), 1.92 (3H, s); ^{13}C NMR ($CDCl_3$) δ 176.5, 167.3, 144.8, 133.8, 132.8, 130.4, 130.3, 129.2, 125.9, 122.8, 119.3, 117.3, 28.4, 23.7, 22.1; MS *m*/*z* 92 (100), 316 (M^+), 318 (M + 2); IR ν_{max} (cm^{-1}) 2916, 1584, 1547, 1434, 1340, 1264, 747, 677. Anal. Calcd for $C_{15}H_{13}BrN_2O$: C, 56.80%; H, 4.13%; N, 8.83%. Found: C, 56.73%; H, 4.19%; N, 8.80%.

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Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectra of all the products and parts of HPLC spectra of **6a**, **6n**, **6q**, **9e**, **9l**, **11d**, **13a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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