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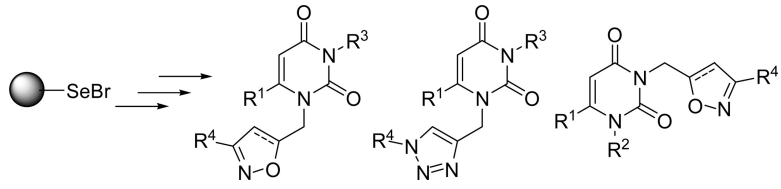

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Solid-Phase Synthesis of Heterocyclic Nucleoside Analogues: Substituted Uracils Tethered to Isoxazoles, Isoxazolines, and Triazoles from a Selenopolystyrene Resin

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A heterocyclic nucleoside analogue library of uracils N1 tethered to isoxazoles, isoxazolines, and triazoles and uracil N3 tethered to isoxazolines and isoxazoles was constructed by solid-phase organic synthesis. This strategy opens the way for the generation of small libraries of heterocyclic nucleoside analogues for biological screening.

Introduction

The cornerstone of combinatorial chemistry is the design of analogue libraries using chemistry which allows for the incorporation of two or more elements of diversification. Solid-phase combinatorial chemistry has been successfully applied in the preparation of many chemical compound libraries, and over the past few years, a large variety of solid-phase reactions have been developed.[1]

In the last two decades, nucleosides and nucleotides have become an important subject of research in the field of medicinal chemistry. The structural modifications of natural nucleosides offer important synthetic routes for the preparation of new bioactive nucleoside analogues.[2] Extensive modifications have been performed on both the heterocyclic base as well as on the sugar moiety.[3] Recently, nucleoside analogues in which the furanose ring has been substituted by heterocyclic moieties[4] have attracted special interests by virtue of their biological action as antiviral and anticancer agents. Among them, uracils tethered to isoxazolines,[5] isoxazoles,[6] and triazoles[7] have been reported frequently and some show a potential antiviral and anticancer activity. For instance, substituted uracil N1 tethered to isoxazoline **1**[5b] was found to be a potential antiviral agent and the isoxazole **2**[6a] was reported to show potent antiviral activities against the Polio virus, while the triazoles **3**[7a] and the isoxazoline **4**[5d] displayed a potent anti-HIV activity (Figure 1).

Because of potential biological and pharmacological applications of these bis-heterocyclic compounds, it is considered worthwhile to develop a general and effective method for the synthesis of uracil tethered to isoxazoles, isoxazolines, and triazoles. However, to the best of our knowledge, there has not been any solid-phase syntheses of both uracil N1 and N3 tethered to isoxazoles, isoxazolines, and triazoles.

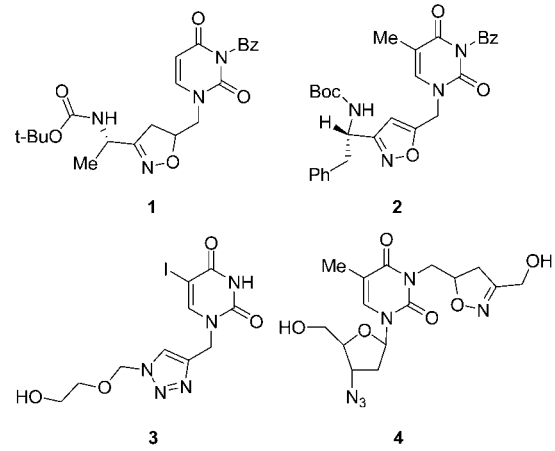

Figure 1

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, several research groups[10] including ours[11] were interested in the preparation of heterocyclic libraries from organoselenium resins. In a continuation of our efforts toward the solid-phase synthesis of low molecular weight heterocycles, we describe, herein, an efficient strategy for the preparation of uracils N1/N3 tethered to isoxazoles, isoxazolines, and triazoles from a selenopolystyrene resin, with the advantages of straightforward synthetic operation, lack of odor and good stability of the supported selenium species, and high purities of the products.

Results and Discussion

Polystyrene-supported selenenyl bromide[9a] (resin **5**) (Br: 1.18 mmol/g) was smoothly reacted with α,β-unsaturated ester in the presence of $ZnCl_2$ at room temperature to afford the corresponding resin-bound 3-bromo-2-seleno ester, which was reacted with primary amine in one pot[12] to give the corresponding yellow resins **6**. The Fourier transform infrared (FT-IR) spectrum showed a strong peak of the carbonyl

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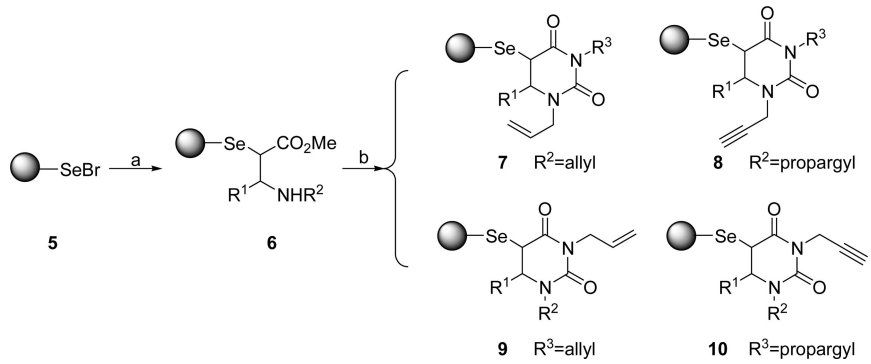
Scheme 1[a]



[a] Reagents and conditions: (a) $ZnCl_2$, $R^1CH{=}CHCO_2Me$, CH_2Cl_2, r.t., 0.5 h, then R^2NH_2, 24 h; (b) K_2CO_3, R^3NCO, DMF, 65 °C, 5h.

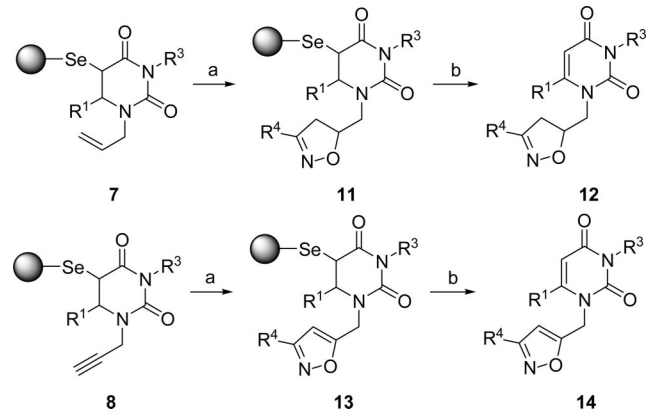
absorptions at 1729−1734 cm^{-1}, and prolonging the reaction time did not cause any increase of the carbonyl peak. It should be noted that the hindrance of R^1 significantly reduced the efficiency of the loading step. When R^1 was H or Me, the reaction gave good results, but in case of a bulky group and aryl, i.e. isopropyl and phenyl, the reaction failed to afford the resin **6** (no carbonyl peak at all). Then in the presence of K_2CO_3, resins **6** were reacted with isocyanates in DMF at 65 °C for 5 h to afford the corresponding resin-bound N1/N3-allyl/propargyl 5,6-dihydrouracils **7**−**10** (Scheme 1).[13] The FT-IR spectrum showed two strong peaks for the carbonyl absorptions at 1729−1734 and 1665−1679 cm^{-1}, respectively. The cyclization reaction proceeded smoothly when R^2 was alkyl and R^3 was alkyl or aryl group. It was the basis of the synthesis of both uracil N1 and N3 tethered to heterocyclic nucleoside analogues that substituents on N1 and N3 came from different components (amines and isocyanates).

With resins **7**−**10** in hand, 1,3-dipolar cycloaddition reaction was performed to form the heterocyclic moieties. Initially, we examined the 1,3-dipolar cycloaddition reaction of resins **7** with nitrile oxides. According to the classical method,[14] resins **7** was allowed to react with nitrile oxides generated in situ from oximes and *N*-chlorosuccinimide (NCS) in the presence of triethylamine to form the isoxazoline resins **11**, which exhibited a weaker C=N stretching band at 1606−1620 cm^{-1}. As expected, the treatment of the newly loaded resins with excess 30% hydrogen peroxide at room temperature resulted in the facile oxidation of the selenide to the corresponding selenoxide. Spontaneous elimination of the selenoxide led to the release of uracil N1 tethered to isoxazolines **12** (Scheme 2) in moderate to good yield with good levels of purity (Table 1). Under the same reaction conditions, the 1,3-dipolar cycloaddition reaction of resins **8** with nitrile oxides gave the isoxazole-supported selenium resins **13** (FTIR: 1635 cm^{-1} with the disappearance of 3297 cm^{-1}), and cleavage of resins **13** gave uracil N1-tethered isoxazoles **14** (Scheme 2, Table 1). The yields and purities were good in most cases except for **14k** and **14l**, in which R^3 was bulky group. In agreement with analogous cycloaddition processes, the reaction showed a complete regioselectivity and the 5-isomer was obtained as the sole product.[15]

In addition to nitrile oxides, azides could perform 1,3-dipolar cycloadditions easily. In the presence of CuI, resins **8** reacted smoothly with alkyl halides and sodium azide through a one-pot 1,3-dipolar cycloaddition[16] to furnish the resin-bound triazoles **15**, while in the case of aryl halides, L-proline and Et_3N were needed. The cleavage of resins **15** afforded the substituted uracils N1 tethered to 1,2,3-triazoles **16** (Scheme 3, Table 2).

Besides uracil N1-tethered heterocycles, uracil N3-tethered to heterocycles are also attractive nucleoside analogues. By

Scheme 2[a]



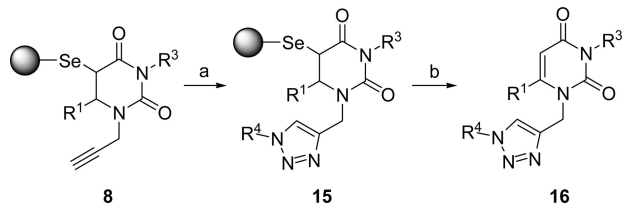
[a] Reagents and conditions: (a) $R^4CH{=}NOH$, NCS, Et_3N, CH_2Cl_2, r.t., 24 h; (b) H_2O_2, THF, r.t., 1 h.

Table 1. Synthesis of Substituted Uracils N1 Tethered to Isoxazolines **12a**−**g** and Isoxazoles **14a**−**l**

product	R^1	R^3	R^4	yield (%)[a]	purity (%)[b]
12a	H	*n*-Bu	4-$MeOC_6H_4$	71	83
12b	H	*n*-Bu	4-FC_6H_4	68	94
12c	H	*n*-Bu	4-ClC_6H_4	70	81
12d	H	*n*-Bu	2-BrC_6H_4	65	87
12e	H	Ph	4-$MeOC_6H_4$	62	87
12f	H	4-$MeOC_6H_4$	4-$MeOC_6H_4$	60	94
12g	H	3-ClC_6H_4	4-$MeOC_6H_4$	58	91
14a	H	*n*-Bu	4-$MeOC_6H_4$	74	96
14b	H	*n*-Bu	4-FC_6H_4	67	89
14c	H	*n*-Bu	4-ClC_6H_4	72	80
14d	H	*n*-Bu	4-BrC_6H_4	68	88
14e	H	Ph	4-$MeOC_6H_4$	64	87
14f	H	4-MeC_6H_4	4-$MeOC_6H_4$	62	84
14g	H	4-$MeOC_6H_4$	4-$MeOC_6H_4$	60	89
14h	H	3-ClC_6H_4	4-$MeOC_6H_4$	59	83
14i	Me	*n*-Bu	4-$MeOC_6H_4$	52	87
14j	H	3-MeC_6H_4	3-BrC_6H_4	57	81
14k	H	2-MeC_6H_4	4-ClC_6H_4	49	76
14l	H	*i*-Pr	4-BrC_6H_4	41	64

[a] Yield of the crude product based on the loading of the resin **5**. [b] Determined by HPLC.

Scheme 3[a]



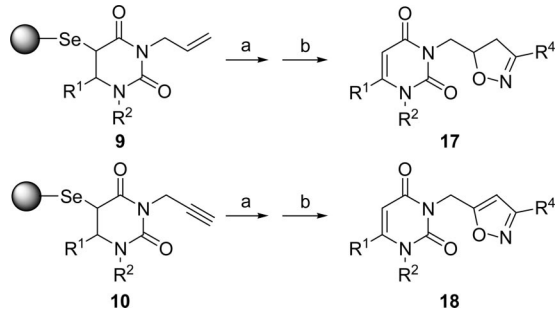
[a] Reagents and conditions: (a) method A NaN_3, R^4X, CuI, DMSO, 65 °C, 15 h; method B NaN_3, R^4I, CuI, L-proline, Et_3N, DMSO, 65 °C, 15 h; (b) H_2O_2, THF, r.t., 1 h.

Table 2. Synthesis of Substituted Uracils N1 Tethered to 1,2,3-Triazoles **16a**−**h**

product	R^1	R^3	R^4X	yield (%)[a]	purity (%)[b]
16a[c]	H	*n*-Bu	MeI	74	93
16b[c]	H	*n*-Bu	BnBr	72	91
16c[c]	H	*n*-Bu	4-$NO_2C_6H_4CH_2Br$	69	82
16d[d]	H	*n*-Bu	PhI	65	89
16e[d]	H	*n*-Bu	4-ClC_6H_4I	61	86
16f[d]	H	Ph	PhI	59	88
16g[c]	H	4-MeC_6H_4	BnBr	62	95
16h[c]	H	4-$MeOC_6H_4$	BnBr	60	89

[a] Yield of the crude product based on the loading of the resin **5**. [b] Determined by HPLC. [c] Prepared by method A. [d] Prepared by method B.

Scheme 4[a]



[a] Reagents and conditions: (a) $R^4CH{=}NOH$, NCS, CH_2Cl_2, Et_3N, r.t., 24 h; (b) H_2O_2, THF, r.t., 1 h.

Table 3. Synthesis of Substituted Uracils N3 Tethered to Isoxazolines **17a**−**e** and Isoxazoles **18a**−**f**

product	R^1	R^2	R^4	yield (%)[a]	purity (%)[b]
17a	H	$PhCH_2CH_2$	4-$MeOC_6H_4$	75	94
17b	H	Bn	4-FC_6H_4	69	88
17c	H	Bn	4-ClC_6H_4	73	93
17d	H	Bn	4-BrC_6H_4	70	89
17e	H	*n*-Pr	4-$MeOC_6H_4$	72	88
18a	H	*n*-Pr	4-$MeOC_6H_4$	74	93
18b	H	Bn	4-BrC_6H_4	70	94
18c	H	$PhCHCH_3$	4-$MeOC_6H_4$	66	86
18d	Me	*n*-Pr	4-$MeOC_6H_4$	61	94
18e	Me	*n*-Pr	3-BrC_6H_4	57	87
18f	H	cyclopropyl	4-BrC_6H_4	60	83

[a] Yield of the crude product based on the loading of the resin **5**. [b] Determined by HPLC.

the same strategy, uracil N3 tethered to isoxazolines **17** and isoxazoles **18** were obtained from resins **9** and **10** in moderate to good yield with good levels of purity (Scheme 4, Table 3).

Conclusions

In summary, we have developed an efficient solid-phase parallel synthetic route to a bis-heterocycle library of uracils N1 tethered to isoxazoles, isoxazolines, and triazoles and uracil N3 tethered to isoxazolines and isoxazoles 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. The easy workup procedure makes the method suitable for building the parallel libraries.

Experimental Section

The melting points were uncorrected. Starting materials were obtained from commercial suppliers and used without further purification. CH_2Cl_2, DMF, and DMSO were distilled from CaH_2 immediately prior to use. Polystyrene (H 1000, 100−200 mesh, cross-linked with 1% divinylbenzene) was purchased from commercial sources. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal standard; chemical shifts were quoted in parts per million, and *J* values were given in hertz. Mass spectra (EI, 70 eV) were recorded on an Agilent 5975 inert mass selective detector. Electrospray ionization (ESI) mass spectra were recorded on a Thero Finigan Deca xp instrument. Infrared spectra were recorded on a Bruker Vector22 spectrometer. HPLC was performed on an Agilent 1100 high performance liquid chromatograph (HPLC). Elemental analyses (EAs) were performed on a Flash EA1110 instrument. High resolution mass spectrometry (HRMS) was performed on a Waters Micromass GCT instrument. Purities of the products are determined by the crude products. Yields are calculated by mass recovery of the crude products based on the loading of the resin **5**. NMR, MS, FT-IR, EA, and the melting points are determined by the purified products (the crude products were subjected to thin-layer chromatography (TLC) on silica gel with ethyl acetate and light petroleum (1:1−1:9) as eluent to give the purified products). The chromatographic conditions (HPLC) were as follows: Column dp 5 μ 250 × 4.6 mm. Mobile phase MeOH: Flow rate 1.0 mL/min. Detector UV 254 nm.

Typical Procedure for the Preparation of Dihydrouracils Supported Selenium Resins 7−10. To a suspension of the swollen polystyrene-supported selenenyl bromide resin **5**[9a] (1.0 g, 1.18 mmol Br/g) in CH_2Cl_2 (10 mL) was added $ZnCl_2$ (0.2 mmol) and α,β-unsaturated ester (3 mmol), and the mixture was stirred for 0.5 h at room temperature. Then, primary amine (6 mmol) was added. After 24 h, the resin was collected by filtration and washed successively with H_2O (20 mL × 2), THF (10 mL × 2), DMF (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) and then dried under vacuum overnight to afford resin **6**. The reaction mixture of dried resin **6** (1.0 g), isocyanate (3.0 mmol) and K_2CO_3 (0.5 mmol) in DMF (15 mL) was stirred for 5 h at 65 °C. Then the resin was collected by filtration and washed successively with H_2O (20 mL × 2), THF (10 mL × 2), DMF (10 mL × 2), THF (10 mL × 2), CH_2Cl_2 (10 mL × 2) to afford resins **7**−**10**.

Typical Procedure for the Preparation of Uracils Tethered to Isoxazolines 12 and 17 and isoxazoles 14 and 18 (Products 12a−g, 14a−l, 17a−e, and 18a−f). Under a positive pressure of nitrogen, to a suspension of the swollen resin **7**−**10** (0.6 g) in CH_2Cl_2 (15 mL) was added

a solution of hydroximoyl halide (2.5 mmol) in CH_2Cl_2 (15 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 was collected by filtration and washed with DMF (10 mL × 3), THF (10 mL × 2), H_2O (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2).

The washed resin was suspended in THF (15 mL), 30% H_2O_2 (0.5 mL) was added, and the mixture was stirred for 1 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 **12**, **14**, **17**, and **18**.

12a: pale solid, mp 131−133 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.34−1.40 (2H, m), 1.54−1.58 (2H, m), 3.21 (1H, dd, J_1 = 16.9 Hz, J_2 = 6.2 Hz), 3.53 (1H, dd, J_1 = 16.9 Hz, J_2 = 10.6 Hz), 3.84 (1H, dd, J_1 = 14.4 Hz, J_2 = 7.0 Hz), 3.89 (3H, s), 3.94 (2H, t, J = 7.5 Hz), 4.15 (1H, dd, J_1 = 14.4 Hz, J_2 = 2.4 Hz), 5.03−5.06 (1H, m), 5.77 (1H, d, J = 7.9 Hz), 6.96 (2H, d, J = 8.7 Hz), 7.35 (1H, d, J = 7.9 Hz), 7.61 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 162.8, 161.3, 156.4, 151.8, 143.1, 128.2, 121.1, 114.2, 101.6, 78.2, 55.3, 51.8, 41.0, 37.9, 29.4, 20.0, 13.7; MS (ESI) m/z 358 $[M + H]^+$; IRυ_{max} (cm^{-1}) 2958, 1705, 1663, 1454, 1254. Elemental analysis calcd. for $C_{19}H_{23}N_3O_4$, C 63.85%; H 6.49%; N 11.76%. Found C 63.78%; H 6.52%; N 11.71%.

12b: pale solid, mp 105−107 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 7.3 Hz), 1.25−1.32 (2H, m), 1.43−1.50 (2H, m), 3.16 (1H, dd, J_1 = 17.0 Hz, J_2 = 6.4 Hz), 3.46 (1H, dd, J_1 = 17.0 Hz, J_2 = 10.7 Hz), 3.79 (1H, dd, J_1 = 14.4 Hz, J_2 = 6.9 Hz), 3.86 (2H, t, J = 7.8 Hz), 4.08 (1H, dd, J_1 = 14.4 Hz, J_2 = 2.7 Hz), 4.99−5.03 (1H, m), 5.70 (1H, d, J = 7.9 Hz), 7.07 (2H, t, J = 8.6 Hz), 7.27 (1H, d, J = 8.0 Hz), 7.58−7.62 (2H, m); ^{13}C NMR ($CDCl_3$) δ 165.2, 162.7, 162.6, 155.9, 151.8, 143.0, 128.7, 128.6, 124.9, 124.8, 116.1, 115.9, 101.8, 78.6, 51.8, 41.0, 37.8, 29.4, 20.0, 13.7; MS (ESI) m/z 346 $[M + H]^+$; IRυ_{max} (cm^{-1}) 2959, 1706, 1662, 1453, 1233. HRMS (MALDI): m/z calcd for $C_{18}H_{21}N_3O_3F$: 346.1562; found: 346.1564.

12c: pale solid, mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7.3 Hz), 1.26−1.34 (2H, m), 1.46−1.52 (2H, m), 3.18 (1H, dd, J_1 = 17.0 Hz, J_2 = 6.4 Hz), 3.48 (1H, dd, J_1 = 17.0 Hz, J_2 = 10.8 Hz), 3.82 (1H, dd, J_1 = 14.4 Hz, J_2 = 6.9 Hz), 3.86 (2H, t, J = 7.7 Hz), 4.11 (1H, dd, J_1 = 14.4 Hz, J_2 = 2.5 Hz), 5.03−5.06 (1H, m), 5.73 (1H, d, J = 7.9 Hz), 7.29 (1H, d, J = 7.9 Hz), 7.38 (2H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 162.7, 156.0, 151.8, 143.0, 136.5, 129.0, 127.9, 127.1, 101.8, 78.8, 51.8, 41.0, 37.6, 29.4, 20.0, 13.7; MS (ESI) m/z 362 $[M + H]^+$, 364 $[M + 2 + H]^+$; IRυ_{max} (cm^{-1}) 2959, 1708, 1663, 1453, 1243. Elemental analysis calcd. for $C_{18}H_{20}ClN_3O_3$, C 59.75%; H 5.57%; N 11.61%. Found C 59.81%; H 5.50%; N 11.67%.

12d: pale solid, mp 88−90 °C; ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz), 1.30−1.36 (2H, m), 1.50−1.58 (2H, m), 3.36 (1H, dd, J_1 = 17.5 Hz, J_2 = 6.2 Hz), 3.62 (1H, dd, J_1 = 17.5 Hz, J_2 = 10.7 Hz), 3.87−3.93 (3H, m), 4.11 (1H, dd, J_1 = 14.4 Hz, J_2 = 2.6 Hz), 5.06−5.10 (1H, m), 5.75 (1H, d, J = 8.0 Hz), 7.26−7.45 (4H, m), 7.62 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 162.7, 157.8, 151.7, 143.1, 133.7, 131.2, 130.6, 130.3, 127.6, 121.7, 101.7, 79.0, 51.5, 41.0, 40.2, 29.5, 20.0, 13.7; MS (ESI) m/z 406 $[M + H]^+$, 408 $[M + 2 + H]^+$; IRυ_{max} (cm^{-1}) 2959, 1708, 1663, 1452, 1244. Elemental analysis calcd. for $C_{18}H_{20}BrN_3O_3$, C 53.21%; H 4.96%; N 10.34%. Found C 53.17%; H 5.01%; N 10.39%.

12e: pale solid, mp 231−233 °C; ^{1}H NMR ($CDCl_3$) δ 3.21 (1H, dd, J_1 = 16.9 Hz, J_2 = 5.8 Hz), 3.46 (1H, dd, J_1 = 16.9 Hz, J_2 = 10.6 Hz), 3.81−3.87 (4H, m), 4.10 (1H, dd, J_1 = 14.4 Hz, J_2 = 2.4 Hz), 5.01−5.04 (1H, m), 5.86 (1H, d, J = 8.0 Hz), 6.93 (2H, d, J = 8.7 Hz), 7.05−7.08 (2H, m), 7.39−7.47 (4H, m), 7.59 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 162.9, 161.5, 156.6, 152.0, 144.1, 134.9, 129.4, 128.8, 128.4, 128.1, 121.1, 114.3, 102.2, 78.2, 55.4, 52.2, 38.1; MS (ESI) m/z 378 $[M + H]^+$; IRυ_{max} (cm^{-1}) 2923, 1715, 1663, 1443, 1254. Elemental analysis calcd. for $C_{21}H_{19}N_3O_4$, C 66.83%; H 5.07%; N 11.13%. Found C 66.75%; H 5.13%; N 11.09%.

12f: pale solid, mp 209−211 °C; ^{1}H NMR ($CDCl_3$) δ 3.19 (1H, dd, J_1 = 16.9 Hz, J_2 = 5.9 Hz), 3.44 (1H, dd, J_1 = 16.9 Hz, J_2 = 10.6 Hz), 3.78−3.85 (7H, m), 4.07 (1H, dd, J_1 = 14.3 Hz, J_2 = 2.4 Hz), 5.00−5.02 (1H, m), 5.83 (1H, d, J = 8.0 Hz), 6.92−6.96 (6H, m), 7.39 (1H, d, J = 8.0 Hz), 7.58 (2H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 162.8, 161.1, 159.2, 156.3, 151.9, 143.7, 128.7, 128.1, 127.1, 120.8, 114.3, 114.0, 101.7, 77.8, 55.1, 51.8, 37.8, 28.9; MS (ESI) m/z 408 $[M + H]^+$; IRυ_{max} (cm^{-1}) 2925, 1714, 1660, 1445, 1254. Elemental analysis calcd. for $C_{22}H_{21}N_3O_5$, C 64.86%; H 5.20%; N 10.31%. Found C 64.89%; H 5.23%; N 10.31%.

12g: pale solid, mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 3.20 (1H, dd, J_1 = 16.9 Hz, J_2 = 5.5 Hz), 3.43 (1H, dd, J_1 = 16.9 Hz, J_2 = 10.7 Hz), 3.81−3.87 (4H, m), 4.02 (1H, dd, J_1 = 14.4 Hz, J_2 = 2.0 Hz), 4.97−5.00 (1H, m), 5.81 (1H, d, J = 8.0 Hz), 6.91−6.96 (4H, m), 7.35−7.40 (3H, m), 7.57 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 162.4, 161.3, 156.5, 151.5, 144.3, 135.8, 134.5, 130.1, 128.9, 128.5, 128.2, 126.5, 120.8, 114.2, 101.8, 77.9, 55.2, 52.0, 37.9; MS (ESI) m/z 412 $[M + H]^+$, 414 $[M + 2 + H]^+$; IRυ_{max} (cm^{-1}) 2923, 1716, 1666, 1441, 1254. Elemental analysis calcd. for $C_{21}H_{18}ClN_3O_4$, C 61.24%; H 4.41%; N 10.20%. Found C 61.23%; H 4.47%; N 10.17%.

14a: oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.33−1.40 (2H, m), 1.58−1.62 (2H, m), 3.85 (3H, s), 3.92 (2H, t, J = 7.8 Hz), 5.04 (2H, s), 5.79 (1H, d, J = 7.9 Hz), 6.58 (1H, s), 6.96 (2H, d, J = 8.8 Hz), 7.31 (1H, d, J = 7.9 Hz), 7.71 (2H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 165.9, 162.6, 162.5, 161.2, 151.1, 141.3, 128.2, 120.8, 114.4, 102.8, 102.0, 55.3, 43.7, 41.3, 29.6, 20.2, 13.7; MS (EI) m/z 355 (M^+); IRυ_{max} (cm^{-1}) 2959, 1711, 1667, 1454, 1255; HRMS: m/z calcd for $C_{19}H_{21}N_3O_4$: 355.1532; found: 355.1541.

14b: oil; ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, t, J = 7.2 Hz), 1.33−1.40 (2H, m), 1.58−1.63 (2H, m), 3.92 (2H, t, J = 8.0 Hz), 5.06 (2H, s), 5.81 (1H, d, J = 7.9 Hz), 6.61 (1H, s), 7.15 (2H, t, J = 8.4 Hz), 7.31 (1H, d, J = 8.0 Hz), 7.75−7.79 (2H, m); ^{13}C NMR ($CDCl_3$) δ 166.4, 165.2, 162.7, 162.5, 162.0, 151.1, 141.2, 128.8, 128.7, 124.6, 124.5,

116.3, 116.0, 102.9, 102.1, 43.8, 41.3, 29.6, 20.2, 13.7; MS (EI) *m/z* 343 (M^+); IRυ_{max} (cm^{-1}) 2959, 1711, 1667, 1454, 1230; HRMS: *m/z* calcd for $C_{18}H_{18}N_3O_3F$: 343.1332; found: 343.1320.

14c: pale solid, mp 91−93 °C; ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, t, J = 7.3 Hz), 1.33−1.40 (2H, m), 1.56−1.62 (2H, m), 3.93 (2H, t, J = 7.6 Hz), 5.06 (2H, s), 5.81 (1H, d, J = 7.9 Hz), 6.62 (1H, s), 7.31 (1H, d, J = 7.9 Hz), 7.43 (2H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 166.5, 162.5, 161.9, 151.1, 141.2, 136.4, 129.3, 128.1, 126.8, 103.0, 102.1, 43.8, 41.3, 29.6, 20.2, 13.7; MS (EI) *m/z* 359 (M^+), 361 ($M^+ + 2$); IRυ_{max} (cm^{-1}) 2959, 1712, 1667, 1454, 1095. Elemental analysis calcd. for $C_{18}H_{18}ClN_3O_3$, C 60.09%; H 5.04%; N 11.68%. Found C 60.08%; H 5.35%; N 11.74%.

14d: pale solid, mp 94−96 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.33−1.39 (2H, m), 1.56−1.62 (2H, m), 3.92 (2H, t, J = 7.6 Hz), 5.07 (2H, s), 5.80 (1H, d, J = 7.9 Hz), 6.63 (1H, s), 7.34 (1H, d, J = 7.9 Hz), 7.58 (2H, d, J = 8.4 Hz), 7.64 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 166.6, 162.5, 161.9, 151.1, 141.3, 132.2, 128.3, 127.2, 124.7, 102.8, 102.0, 43.8, 41.3, 29.6, 20.1, 13.7; MS (EI) *m/z* 403 (M^+), 405 ($M^+ + 2$); IRυ_{max} (cm^{-1}) 2959, 1710, 1666, 1454; HRMS: *m/z* calcd for $C_{18}H_{18}BrN_3O_3$: 403.0532; found: 403.0535.

14e: oil; ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s), 5.06 (2H, s), 5.93 (1H, d, J = 8.0 Hz), 6.61 (1H, s), 6.96 (2H, d, J = 8.8 Hz), 7.22 (2H, d, J = 7.4 Hz), 7.43−7.52 (4H, m), 7.71 (2H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 165.5, 162.6, 162.5, 161.2, 151.3, 142.1, 134.7, 129.4, 128.9, 128.2, 128.1, 120.7, 114.4, 103.2, 102.5, 55.3, 43.7; MS (EI) *m/z* 375 (M^+); IRυ_{max} (cm^{-1}) 2926, 1717, 1670, 1436, 1254; HRMS: *m/z* calcd for $C_{21}H_{17}N_3O_4$: 375.1219; found: 375.1228.

14f: pale solid, mp 188−190 °C; ^{1}H NMR ($CDCl_3$) δ 2.39 (3H, s), 3.85 (3H, s), 5.06 (2H, s), 5.93 (1H, d, J = 8.0 Hz), 6.61 (1H, s), 6.96 (2H, d, J = 8.8 Hz), 7.10 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 8.1 Hz), 7.43 (1H, d, J = 8.0 Hz), 7.71 (2H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 165.5, 162.7, 162.6, 161.2, 151.4, 142.0, 138.9, 132.0, 130.2, 128.2, 127.8, 120.7, 114.4, 103.2, 102.5, 55.3, 43.7, 21.2; MS (EI) *m/z* 389 (M^+); IRυ_{max} (cm^{-1}) 2924, 1717, 1666, 1436, 1254; HRMS: *m/z* calcd for $C_{22}H_{19}N_3O_4$: 389.1376; found: 389.1384.

14g: pale solid, mp 183−185 °C; ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 3.84 (3H, s), 5.04 (2H, s), 5.90 (1H, d, J = 8.0 Hz), 6.61 (1H, s), 6.94−7.00 (4H, m), 7.13 (2H, d, J = 8.9 Hz), 7.41 (1H, d, J = 8.0 Hz), 7.71 (2H, d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 165.6, 162.9, 162.5, 161.2, 159.6, 151.5, 142.1, 129.1, 128.2, 127.2, 120.7, 114.8, 114.4, 103.1, 102.4, 55.4, 55.3, 43.8; MS (EI) *m/z* 405 (M^+); IRυ_{max} (cm^{-1}) 2923, 1718, 1667, 1437, 1254; HRMS: *m/z* calcd for $C_{22}H_{19}N_3O_5$: 405.1325; found: 405.1318.

14h: oil; ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s), 5.07 (2H, s), 5.93 (1H, d, J = 8.1 Hz), 6.62 (1H, s), 6.97 (2H, d, J = 8.8 Hz), 7.11−7.15 (1H, m), 7.25−7.26 (1H, m), 7.41−7.46 (3H, m), 7.72 (2H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 165.2, 162.6, 162.3, 161.3, 151.0, 142.3, 135.6, 134.9, 130.3, 129.3, 128.7, 128.2, 126.6, 120.6, 114.4, 103.2, 102.5, 55.3, 43.7; MS (EI) *m/z* 409 (M^+), 411 ($M^+ + 2$); IRυ_{max} (cm^{-1}) 2926, 1719, 1669, 1435, 1253; HRMS: *m/z* calcd for $C_{21}H_{16}N_3O_4Cl$: 409.0829; found: 409.0836.

14i: oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.33−1.39 (2H, m), 1.57−1.62 (2H, m), 2.40 (3H, s), 3.85 (3H, s), 3.92 (2H, t, J = 7.3 Hz), 5.16 (2H, s), 5.68 (1H, s), 6.59 (1H, s), 6.96 (2H, d, J = 8.6 Hz), 7.72 (2H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 166.5, 162.3, 161.8, 161.0, 151.8, 150.4, 128.1, 120.7, 114.2, 102.5, 101.7, 55.2, 41.3, 39.8, 29.5, 20.1, 19.8, 13.7; MS (EI) *m/z* 369 (M^+); IRυ_{max} (cm^{-1}) 2959, 1701, 1663, 1429; HRMS (MALDI): *m/z* calcd for $C_{20}H_{24}N_3O_4$: 370.1761; found: 370.1751.

14j: oil; ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s), 5.08 (2H, s), 5.95 (1H, d, J = 8.0 Hz), 6.66 (1H, s), 7.00−7.02 (2H, m), 7.24 (1H, d, J = 7.7 Hz), 7.31−7.40 (2H, m), 7.43 (1H, d, J = 8.0 Hz), 7.58 (1H, d, J = 8.2 Hz), 7.70 (1H, d, J = 7.8 Hz), 7.94 (1H, s); ^{13}C NMR ($CDCl_3$) δ 166.2, 162.6, 161.7, 151.3, 141.9, 139.5, 134.4, 133.3, 130.5, 130.2, 129.9, 129.8, 129.3, 128.5, 125.3, 125.0, 123.0, 103.3, 102.6, 43.8, 21.3; MS (EI) *m/z* 437 (M^+), 439 ($M^+ + 2$); IRυ_{max} (cm^{-1}) 2924, 1717, 1664, 1443, 754; HRMS: *m/z* calcd for $C_{21}H_{16}BrN_3O_3$: 437.0375; found: 437.0371.

14k: oil; ^{1}H NMR ($CDCl_3$) δ 2.11 (3H, s), 5.07 (1H, d, J = 15.6 Hz), 5.12 (1H, d, J = 15.6 Hz), 5.95 (1H, d, J = 8.0 Hz), 6.65 (1H, s), 7.11 (1H, d, J = 7.3 Hz), 7.30−7.47 (6H, m), 7.71 (2H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 166.2, 162.2, 162.0, 150.8, 142.1, 136.4, 135.4, 133.8, 131.1, 129.3, 129.2, 128.1, 128.0, 127.1, 126.7, 103.2, 102.4, 43.8, 17.3; MS (EI) *m/z* 393 (M^+), 395 ($M^+ + 2$); IRυ_{max} (cm^{-1}) 2925, 1721, 1662, 1441, 757; HRMS: *m/z* calcd for $C_{21}H_{16}ClN_3O_3$: 393.0880; found: 393.0883.

14l: oil; ^{1}H NMR ($CDCl_3$) δ 1.47 (6H, d, J = 6.8 Hz), 5.04 (2H, s), 5.16−5.21 (1H, m), 5.77 (1H, d, J = 7.8 Hz), 6.63 (1H, s), 7.28 (1H, d, J = 7.8 Hz), 7.60 (2H, d, J = 8.0 Hz), 7.67 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7, 163.0, 162.0, 150.8, 141.1, 132.2, 128.3, 127.3, 124.7, 103.2, 102.0, 46.0, 43.6, 19.1; MS (EI) *m/z* 389 (M^+), 391 ($M^+ + 2$); IRυ_{max} (cm^{-1}) 2972, 1704, 1656, 1448, 1047; HRMS: *m/z* calcd for $C_{17}H_{16}BrN_3O_3$: 389.0375; found: 389.0377.

17a: pale solid, mp 109−111 °C; ^{1}H NMR ($CDCl_3$) δ 2.99 (2H, t, J = 6.9 Hz), 3.19 (1H, dd, J_1 = 16.0 Hz, J_2 = 5.6 Hz), 3.36 (1H, dd, J_1 = 16.0 Hz, J_2 = 10.0 Hz), 3.83 (3H, s), 3.92−4.07 (3H, m), 4.33 (1H, dd, J_1 = 13.1 Hz, J_2 = 7.2 Hz), 5.04−5.09 (1H, m), 5.57 (1H, d, J = 7.9 Hz), 6.80 (1H, d, J = 7.9 Hz), 6.90 (2H, d, J = 8.7 Hz), 7.15 (2H, d, J = 7.5 Hz), 7.23−7.31 (3H, m), 7.61 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 163.0, 160.9, 156.0, 151.3, 142.9, 137.1, 128.9, 128.8, 128.3, 126.9, 121.9, 114.0, 100.9, 77.0, 55.3, 51.6, 43.6, 38.8, 34.9; MS (ESI) *m/z* 406 $[M + H]^+$; IRυ_{max} (cm^{-1}) 2927, 1708, 1658, 1455, 1254. Elemental analysis calcd. for $C_{23}H_{23}N_3O_4$, C 68.13%; H 5.72%; N 10.36%. Found C 68.16%; H 5.70%; N 10.31%.

17b: oil; ^{1}H NMR ($CDCl_3$) δ 3.21 (1H, dd, J_1 = 16.6 Hz, J_2 = 6.1 Hz), 3.39 (1H, dd, J_1 = 16.6 Hz, J_2 = 10.4 Hz), 4.06 (1H, dd, J_1 = 13.2 Hz, J_2 = 5.7 Hz), 4.37 (1H, dd, J_1 = 13.2 Hz, J_2 = 7.4 Hz), 4.89 (1H, d, J = 14.9 Hz), 4.99 (1H, d, J = 14.9 Hz), 5.12−5.16 (1H, m), 5.75 (1H, d, J = 7.9 Hz), 7.07 (2H, t, J = 8.6 Hz), 7.17 (1H, d, J = 7.9 Hz), 7.26−7.40 (5H, m), 7.64−7.68 (2H, m); ^{13}C NMR ($CDCl_3$) δ 164.9, 162.9, 162.4, 155.4, 151.8, 142.1, 135.0, 129.1,

128.7, 128.7, 128.4, 128.0, 125.6, 125.5, 115.8, 115.6, 101.9, 77.4, 52.3, 43.7, 38.7; MS (ESI) *m/z* 380 $[M + H]^+$; IRυ_{max} (cm^{-1}) 2925, 1709, 1660; HRMS (MALDI): *m/z* calcd for $C_{21}H_{19}N_3O_3F$: 380.1405; found: 380.1408.

17c: pale solid, mp 155−157 °C; ^{1}H NMR ($CDCl_3$) δ 3.20 (1H, dd, J_1 = 16.7 Hz, J_2 = 6.2 Hz), 3.37 (1H, dd, J_1 = 16.6 Hz, J_2 = 10.4 Hz), 4.06 (1H, dd, J_1 = 13.2 Hz, J_2 = 5.7 Hz), 4.36 (1H, dd, J_1 = 13.2 Hz, J_2 = 7.3 Hz), 4.90 (1H, d, J = 14.9 Hz), 4.98 (1H, d, J = 14.9 Hz), 5.12−5.17 (1H, m), 5.75 (1H, d, J = 7.9 Hz), 7.18 (1H, d, J = 7.9 Hz), 7.26−7.30 (2H, m), 7.34−7.40 (5H, m), 7.59 (2H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 162.9, 155.5, 151.8, 142.1, 136.0, 135.0, 129.1, 128.8, 128.5, 128.0, 127.8, 101.9, 77.6, 52.3, 43.7, 38.4; MS (ESI) *m/z* 396 $[M + H]^+$, 398 $[M + 2 + H]^+$; IRυ_{max} (cm^{-1}) 3054, 1704, 1657, 1454. Elemental analysis calcd. for $C_{21}H_{18}ClN_3O_3$, C 63.72%; H 4.58%; N 10.62%. Found C 63.68%; H 4.61%; N 10.67%.

17d: pale solid, mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 3.19 (1H, dd, J_1 = 16.7 Hz, J_2 = 6.1 Hz), 3.38 (1H, dd, J_1 = 16.7 Hz, J_2 = 10.4 Hz), 4.05 (1H, dd, J_1 = 13.1 Hz, J_2 = 5.6 Hz), 4.36 (1H, dd, J_1 = 13.1 Hz, J_2 = 7.4 Hz), 4.89 (1H, d, J = 14.9 Hz), 4.98 (1H, d, J = 14.9 Hz), 5.12−5.17 (1H, m), 5.76 (1H, d, J = 7.9 Hz), 7.18 (1H, d, J = 7.9 Hz), 7.26−7.39 (5H, m), 7.51−7.54 (4H, m); ^{13}C NMR ($CDCl_3$) δ 163.0, 155.8, 151.9, 142.3, 135.1, 131.9, 129.2, 128.6, 128.3, 128.2, 128.1, 124.4, 102.0, 77.7, 52.5, 43.8, 38.5; MS (ESI) *m/z* 440 $[M + H]^+$, 442 $[M + 2 + H]^+$; IRυ_{max} (cm^{-1}) 2925, 1706, 1659, 1454. Elemental analysis calcd. for $C_{21}H_{18}BrN_3O_3$, C 57.29%; H 4.12%; N 9.54%. Found C 57.34%; H 4.09%; N 9.57%.

17e: pale solid, mp 89−91 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.69−1.75 (2H, m), 3.22 (1H, dd, J_1 = 16.5 Hz, J_2 = 6.1 Hz), 3.37 (1H, dd, J_1 = 16.5 Hz, J_2 = 10.3 Hz), 3.68−3.75 (2H, m), 3.83 (3H, s), 4.04 (1H, dd, J_1 = 14.2 Hz, J_2 = 5.8 Hz), 4.32 (1H, dd, J_1 = 14.2 Hz, J_2 = 7.2 Hz), 5.06−5.10 (1H, m), 5.74 (1H, d, J = 7.8 Hz), 6.90 (2H, d, J = 8.3 Hz), 7.19 (1H, d, J = 7.8 Hz), 7.61 (2H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 163.2, 161.0, 156.1, 151.6, 142.9, 128.3, 121.9, 114.0, 101.3, 77.2, 55.4, 51.4, 43.7, 38.9, 22.2, 11.0; MS (ESI) *m/z* 344 $[M + H]^+$; IRυ_{max} (cm^{-1}) 2964, 1708, 1660, 1456. Elemental analysis calcd. for $C_{18}H_{21}N_3O_4$, C 62.96%; H 6.16%; N 12.24%. Found C 62.99%; H 6.11%; N 12.28%.

18a: oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7.4 Hz), 1.69−1.75 (2H, m), 3.71 (2H, t, J = 7.2 Hz), 3.83 (3H, s), 5.28 (2H, s), 5.76 (1H, d, J = 7.9 Hz), 6.49 (1H, s), 6.93 (2H, d, J = 8.7 Hz), 7.15 (1H, d, J = 7.9 Hz), 7.69 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 167.4, 162.2, 162.0, 160.8, 150.9, 143.0, 128,0, 121,2, 114.1, 101.0, 55.2, 51.3, 36.0, 22.1, 10.8; MS (EI) *m/z* 341 (M^+); IRυ_{max} (cm^{-1}) 2930, 1712, 1661, 1454; HRMS (MALDI): *m/z* calcd for $C_{18}H_{20}N_3O_4$: 342.1448; found: 342.1451.

18b: pale solid, mp 122−124 °C; ^{1}H NMR ($CDCl_3$) δ 4.95 (2H, s), 5.32 (2H, s), 5.79 (1H, d, J = 7.9 Hz), 6.55 (1H, s), 7.19 (1H, d, J = 7.9 Hz), 7.26−7.38 (5H, m), 7.56 (2H, d, J = 8.3 Hz), 7.64 (2H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 167.9, 162.1, 161.6, 151.3, 142.4, 134.9, 132.1, 129.2, 128.7, 128.3, 128.2, 127.9, 124.3, 102.0, 101.4, 52.5, 36.2; MS (EI) *m/z* 437 (M^+), 439 ($M^+ + 2$); IRυ_{max} (cm^{-1}) 3108, 1708, 1660, 1454. Elemental analysis calcd. for $C_{21}H_{16}BrN_3O_3$, C 57.55%; H 3.68%; N 9.59%. Found C 57.50%; H 3.67%; N 9.64%.

18c: pale solid, mp 86−88 °C; ^{1}H NMR ($CDCl_3$) δ 1.70 (3H, d, J = 7.0 Hz), 3.84 (3H, s), 5.29 (1H, d, J = 15.2 Hz), 5.34 (1H, d, J = 15.2 Hz), 5.74 (1H, d, J = 8.1 Hz), 5.99 (1H, q, J = 7.0 Hz), 6.53 (1H, s), 6.95 (2H, d, J = 8.6 Hz), 7.06 (1H, d, J = 8.1 Hz), 7.31−7.41 (5H, m), 7.71 (2H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 167.4, 162.1, 161.9, 160.9, 151.3, 139.6, 138.6, 129.2, 128.6, 128.2, 127.3, 121.4, 114.2, 101.9, 101.3, 55.4, 54.6, 36.3, 18.6; MS (EI) *m/z* 403 (M^+); IRυ_{max} (cm^{-1}) 2932, 1711, 1665, 1448, 1252. Elemental analysis calcd. for $C_{23}H_{21}N_3O_4$, C 68.47%; H 5.25%; N 10.42%. Found C 68.51%; H 5.20%; N 10.47%.

18d: pale solid, mp 155−157 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, t, J = 7.4 Hz), 1.65−1.73 (2H, m), 2.26 (3H, s), 3.78 (2H, t, J = 7.8 Hz), 3.84 (3H, s), 5.28 (2H, s), 5.64 (1H, s), 6.49 (1H, s), 6.94 (2H, d, J = 8.7 Hz), 7.70 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 167.6, 162.1, 161.4, 160.9, 152.1, 151.6, 128.2, 121.5, 114.2, 101.5, 101.1, 55.3, 46.9, 36.2, 22.2, 19.9, 11.1; MS (EI) *m/z* 355 (M^+); IRυ_{max} (cm^{-1}) 2963, 1703, 1660, 1433, 1252; HRMS (MALDI): *m/z* calcd for $C_{19}H_{22}N_3O_4$: 356.1605; found: 356.1607.

18e: pale solid, mp 135−137 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, t, J = 7.4 Hz), 1.65−1.73 (2H, m), 2.27 (3H, s), 3.79 (2H, t, J = 7.9 Hz), 5.29 (2H, s), 5.64 (1H, s), 6.52 (1H, s), 7.27−7.32 (1H, m), 7.54 (1H, d, J = 8.0 Hz), 7.70 (1H, d, J = 7.8 Hz), 7.91 (1H, s); ^{13}C NMR ($CDCl_3$) δ 168.3, 161.3, 161.2, 152.1, 151.6, 132.8, 161.0, 130.3, 129.8, 125.3, 122.8, 101.4, 101.2, 46.9, 36.2, 22.2, 19.8, 11.0; MS (EI) *m/z* 403 (M^+), 405 ($M^+ + 2$); IRυ_{max} (cm^{-1}) 2964, 1699, 1656, 1432, 1063. Elemental analysis calcd. for $C_{18}H_{18}BrN_3O_3$, C 53.48%; H 4.49%; N 10.39%. Found C 53.44%; H 4.53%; N 10.36%.

18f: oil; ^{1}H NMR ($CDCl_3$) δ 0.80−0.83 (2H, m), 1.02−1.05 (2H, m), 3.06−3.09 (1H, m), 5.25 (2H, s), 5.73 (1H, d, J = 8.0 Hz), 6.54 (1H, s), 7.23 (1H, d, J = 8.0 Hz), 7.52 (2H, d, J = 7.8 Hz), 7.60 (2H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 167.9, 162.1, 161.6, 151.9, 143.2, 132.0, 128.3, 127.8, 124.2, 101.5, 101.1, 36.0, 32.0, 7.0; MS (EI) *m/z* 387 (M^+), 389 ($M^+ + 2$); IRυ_{max} (cm^{-1}) 3160, 1701, 1658, 1433, 822; HRMS: *m/ z* calcd for $C_{17}H_{14}BrN_3O_3$: 387.0219; found: 387.0221.

Typical Procedure for the Preparation of Uracils N1 Tethered to 1,2,3-Triazoles 16 (Products 16a−h). Method A: Under a positive pressure of nitrogen, to a suspension of the swollen resin **8** (0.6 g) in DMSO (10 mL) was added NaN_3 (4.0 mmol), alkyl bromide (4.0 mmol), and CuI (0.25 mmol). The mixture was stirred at 65 °C for 15 h. The resin **15**(**a**, **b**, **c**, **g**, **h**) was collected by filtration and washed with DMF (10 mL × 3), 0.1 N NH_3 (aq) (10 mL × 2), H_2O (10 mL × 3), and THF (10 mL × 3).

Method B: Under a positive pressure of nitrogen, to a suspension of the swollen resin **8** (0.6 g) in DMSO (10 mL) was added NaN_3 (4.0 mmol), ArI (4.0 mmol), L-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 **15**(**d**, **e**, **f**) was collected by filtration and washed with DMF (10 mL × 3), 0.1 N NH_3 (aq) (10 mL × 2), H_2O (10 mL × 3), and THF (10 mL × 3).

To a suspension of the swollen resins **15** (0.6 g) in THF (15 mL) was added 30% H_2O_2 (0.5 mL), and the mixture was stirred for 1 h at room temperature. The mixture was filtered and the resin was washed with CH_2Cl_2 (10 mL × 2). The filtrate was washed with H_2O (10 mL × 2), dried over $MgSO_4$, and evaporated to dryness in vacuum to obtain the crude products **16**.

16a: oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.33−1.39 (2H, m), 1.54−1.60 (2H, m), 3.90 (2H, t, J = 7.6 Hz), 4.10 (3H, s), 4.99 (2H, s), 5.73 (1H, d, J = 7.9 Hz), 7.47 (1H, d, J = 7.9 Hz), 7.69 (1H, s); ^{13}C NMR ($CDCl_3$) δ 162.7, 151.3, 142.2, 141.8, 124.3, 102.0, 43.9, 40.9, 36.6, 29.4, 20.0, 13.6; MS (EI) m/z 263 (M^+); IRυ_{max} (cm^{-1}) 2958, 1701, 1650, 1453; HRMS: m/z calcd for $C_{12}H_{17}N_5O_2$: 263.1382; found: 263.1392.

16b: oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.28−1.36 (2H, m), 1.51−1.59 (2H, m), 3.88 (2H, t, J = 7.5 Hz), 4.95 (2H, s), 5.51 (2H, s), 5.72 (1H, d, J = 7.9 Hz), 7.27−7.29 (2H, m), 7.36−7.38 (3H, m), 7.43 (1H, d, J = 7.9 Hz), 7.58 (1H, s); ^{13}C NMR ($CDCl_3$) δ 162.8, 151.4, 142.4, 141.8, 134.1, 129.1, 128.9, 128.2, 123.3, 102.2, 54.3, 44.0, 41.1, 29.5, 20.1, 13.7; MS (EI) m/z 339 (M^+); IRυ_{max} (cm^{-1}) 2958, 1702, 1652, 1453; HRMS: m/z calcd for $C_{18}H_{21}N_5O_2$: 339.1695; found: 339.1683.

16c: pale solid, mp 157−159 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.29−1.36 (2H, m), 1.53−1.57 (2H, m), 3.87 (2H, t, J = 7.5 Hz), 5.00 (2H, s), 5.67 (2H, s), 5.74 (1H, d, J = 7.9 Hz), 7.44−7.50 (3H, m), 7.76 (1H, s), 8.21 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 162.6, 151.2, 147.9, 142.8, 141.9, 141.1, 128.6, 124.1, 123.7, 102.0, 53.0, 44.0, 40.9, 29.4, 20.0, 13.6; MS (EI) m/z 384 (M^+); IRυ_{max} (cm^{-1}) 2961, 1703, 1663, 1523, 1458, 1347. Elemental analysis calcd. for $C_{18}H_{20}N_6O_4$, C 56.24%; H 5.24%; N 21.86%. Found C 56.22%; H 5.27%; N 21.89%.

16d: oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.33−1.39 (2H, m), 1.55−1.63 (2H, m), 3.91 (2H, t, J = 7.4 Hz), 5.10 (2H, s), 5.76 (1H, d, J = 7.9 Hz), 7.33−7.57 (4H, m), 7.73 (2H, d, J = 7.7 Hz), 8.18 (1H, s); ^{13}C NMR ($CDCl_3$) δ 162.7, 151.3, 142.7, 141.9, 136.6, 129.6, 128.9, 121.7, 120.4, 102.0, 44.0, 41.0, 29.4, 20.0, 13.6; MS (EI) m/z 325 (M^+); IRυ_{max} (cm^{-1}) 2959, 1703, 1651, 1453; HRMS: m/z calcd for $C_{17}H_{19}N_5O_2$: 325.1539; found: 325.1535.

16e: oil; ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.6 Hz), 1.33−1.39 (2H, m), 1.55−1.63 (2H, m), 3.91 (2H, t, J = 7.5 Hz), 5.07 (2H, s), 5.77 (1H, d, J = 7.9 Hz), 7.49−7.52 (3H, m), 7.68 (2H, d, J = 8.8 Hz), 8.13 (1H, s); ^{13}C NMR ($CDCl_3$) δ 162.8, 151.4, 143.0, 141.9, 135.1, 134.9, 130.0, 121.7, 121.7, 102.3, 44.1, 41.1, 29.6, 20.1, 13.7; MS (EI) m/z 359 (M^+), 361 (M^+ + 2); IRυ_{max} (cm^{-1}) 2959, 1703, 1652, 1455; HRMS: m/z calcd for $C_{17}H_{18}N_5O_2Cl$: 359.1149; found: 359.1152.

16f: pale solid, mp 179−181 °C; ^{1}H NMR ($CDCl_3$) δ 5.09 (2H, s), 5.89 (1H, d, J = 7.9 Hz), 7.21 (2H, d, J = 7.5 Hz), 7.41−7.53 (6H, m), 7.65 (1H, d, J = 7.9 Hz), 7.70 (2H, d, J = 7.8 Hz), 8.14 (1H, s); ^{13}C NMR ($CDCl_3$) δ 162.8, 151.5, 142.8, 142.4, 136.6, 134.7, 129.7, 129.3, 129.0, 128.8, 128.1, 122.1, 120.4, 102.6, 44.2; MS (EI) m/z 345 (M^+); IRυ_{max} (cm^{-1}) 2959, 1716, 1657, 1446; HRMS (MALDI): m/z calcd for $C_{19}H_{16}N_5O_2$: 346.1299; found: 346.1294.

16g: pale solid, mp 215−217 °C; ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 4.96 (2H, s), 5.47 (2H, s), 5.84 (1H, d, J = 8.0 Hz), 7.04 (2H, d, J = 8.2 Hz), 7.25−7.28 (4H, m), 7.35−7.37 (3H, m),7.56 (1H, d, J = 8.0 Hz), 7.59 (1H, s); ^{13}C NMR ($CDCl_3$) δ 162.9, 151.6, 142.7, 142.1, 138.7, 134.1, 132.1, 130.0, 129.1, 128.8, 128.2, 127.7, 123.7, 102.5, 54.3, 44.2, 21.2; MS (EI) m/z 373 (M^+); IRυ_{max} (cm^{-1}) 3130, 1711, 1655, 1443; HRMS (MALDI): m/z calcd for $C_{21}H_{20}N_5O_2$: 374.1612; found: 374.1611.

16h: pale solid, mp 202−204 °C; ^{1}H NMR ($CDCl_3$) δ 3.82 (3H, s), 4.96 (2H, s), 5.49 (2H, s), 5.86 (1H, d, J = 7.9 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.08 (2H, d, J = 8.8 Hz), 7.28 (2H, d, J = 3.6 Hz), 7.36−7.38 (3H, m), 7.57 (1H, d, J = 7.9 Hz), 7.59 (1H, s); ^{13}C NMR ($CDCl_3$) δ 163.1, 159.4, 151.7, 142.8, 142.1, 134.1, 129.1, 129.0, 128.8, 128.2, 127.3, 123.8, 114.6, 102.4, 55.3, 54.2, 44.2; MS (EI) m/z 389 (M^+); IRυ_{max} (cm^{-1}) 2922, 1703, 1657, 1252; HRMS (MALDI): m/z calcd for $C_{21}H_{20}N_5O_3$: 390.1561; found: 390.1558.

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Supporting Information Available. 1H NMR and 13C NMR spectra of all the products and parts of HPLC spectra of **12b**, **14g**, **16b**, **17e**, and **18b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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