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One-step synthesis of *N*-alkyl-2-aryl-2-oxoacetamides and N^2,N^4-dialkyl-2-aryl-4*H*-1,3-benzodioxine-2,4-dicarboxamides

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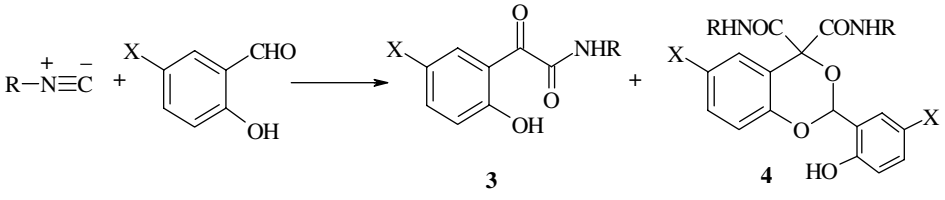
Abstract—Alkyl isocyanides react with 2-hydroxybenzaldehyde or 2-hydroxy-5-nitrobenzaldehyde to afford *N*-alkyl-2-aryl-2-oxoacetamides and N^2,N^4-dialkyl-2-aryl-4*H*-1,3-benzodioxine-2,4-dicarboxamides in nearly 1:1 ratios. Treatment of 2,6-dimethylphenyl isocyanide with 2-hydroxy-5-nitrobenzaldehyde affords only the 2-oxoacetamide derivative.

Multi-component reactions (MCRs) have attracted much attention for combinatorial chemistry.[1] Of pivotal importance in this area are the isocyanide based MCRs such as the versatile *Ugi* and *Passerini* reactions.[1–4] Isocyanides are compounds with an extraordinary functional group; its unusual valence structure and reactivity have been discussed for over one and a half centuries.[4] Isocyanides are the only class of stable organic compounds with a formally divalent carbon. Owing to its reactivity the isocyanide group differs fundamentally from other functional groups. One of the classic themes in the chemistry of isocyanides is heterocyclic synthesis.[5,6] As part of our current studies on the development of new routes to heterocyclic systems,[7] we now report the reaction between alkyl isocyanides 1 and 2-hydroxybenzaldehyde (**2a**) or 2-hydroxy-5-nitrobenzaldehyde (**2b**) in CH_2Cl_2, which leads to 2-oxoacetamides **3** and 4*H*-1,3-benzodioxine derivatives **4** in moderate yields (Scheme 1).



3 **4**

	R	X
1a	*t*-Bu	**2a** H
1b	cyclohexyl	**2b** NO_2
1c	Bn	
1d	2,6-dimethylphenyl	
1e	1,1,3,3-tetramethylbutyl	

	R	X	Yield (%) of **3**	Yield (%) of **4**
3a; 4a	*t*-Bu	H	40	48
3b; 4b	cyclohexyl	H	38	55
3c; 4c	*t*-Bu	NO_2	40	55
3d; 4d	cyclohexyl	NO_2	40	55
3e; 4e	Bn	NO_2	65	30
3f; 4f	1,1,3,3-tetramethylbutyl	NO_2	35	60
3g; -	2,6-dimethylphenyl	NO_2	95	_

Scheme 1.

Keywords: Benzodioxine; 2-Oxoacetamides; Isocyanides; 2-Hydroxybenzaldehyde.
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Isocyanides **1** react with **2a** or **2b** to produce functionalized 2-oxoacetamides **3a–g** together with the 4*H*-1,3-benzodioxine derivatives **4a–f** in CH_2Cl_2 at room temperature (Scheme 1). These products were separated by column chromatography and characterized on the basis of their spectroscopic data.[8]

A single-crystal X-ray diffraction study confirmed the identity of compound **4f**.[9] An ORTEP diagram of **4f** is shown in Figure 1. The crystal structure of **4f**, which had been recrystallized from $CHCl_3$/hexane, is quite interesting. The lattice of the monoclinic crystals[9] includes one molecule of $CHCl_3$ per two molecules of **4f** (see Fig. 2).

In the ^{1}H NMR spectrum of **3a**, the *tert*-butyl group was observed at $\delta = 1.46$ ppm as a singlet, the NH and OH protons appeared at $\delta = 7.02$ ppm and $\delta = 12.01$ ppm, respectively. The ^{13}C NMR spectrum of **3a** showed ten distinct resonances in agreement with the proposed structure. The ^{1}H NMR spectrum of **4a** exhibited two *tert*-butyl groups ($\delta = 1.22$ and 1.41 ppm), one methine group ($\delta = 6.48$ ppm), one hydroxy group ($\delta = 9.54$ ppm), and two NH groups ($\delta = 6.84$ and 8.34 ppm). The proton decoupled ^{13}C NMR spectrum of **4a** showed 20 distinct resonances. The ^{1}H and ^{13}C NMR spectra of **3b–f** and **4b–g** were similar to those for **3a** or **4a** except for the alkyl/aryl regions. Partial assignment of these resonances is given in the Experimental.

On the basis of the well established chemistry of isocyanides,[1–6] it is reasonable to assume that compound **3** results from nucleophilic addition of the isocyanide to the aldehyde group to produce the zwitterionic species **5**, which in the presence of H_2O leads to intermediate **6**. Such a product may oxidize under the reaction conditions employed and produce **3** (Scheme 2).

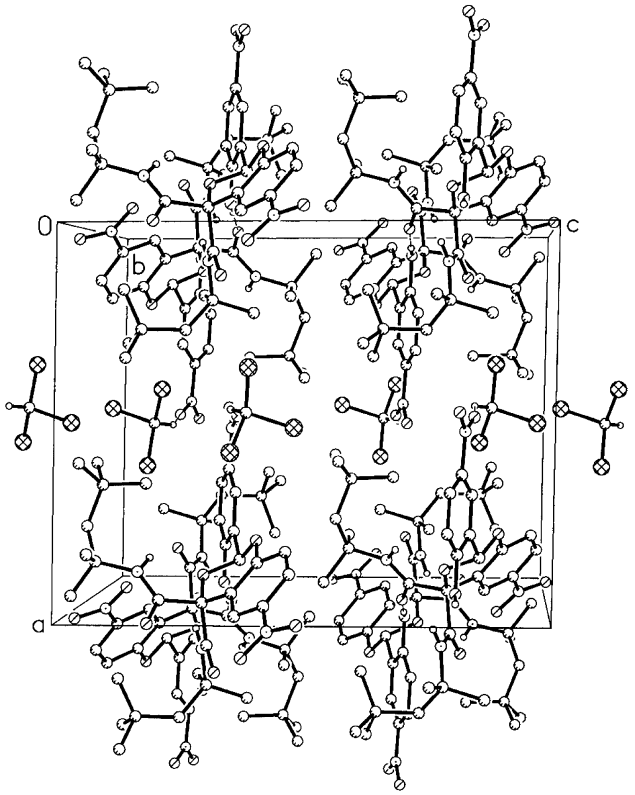


Figure 2. Crystal packing of **4f**, showing chloroform molecules in the unit cell.

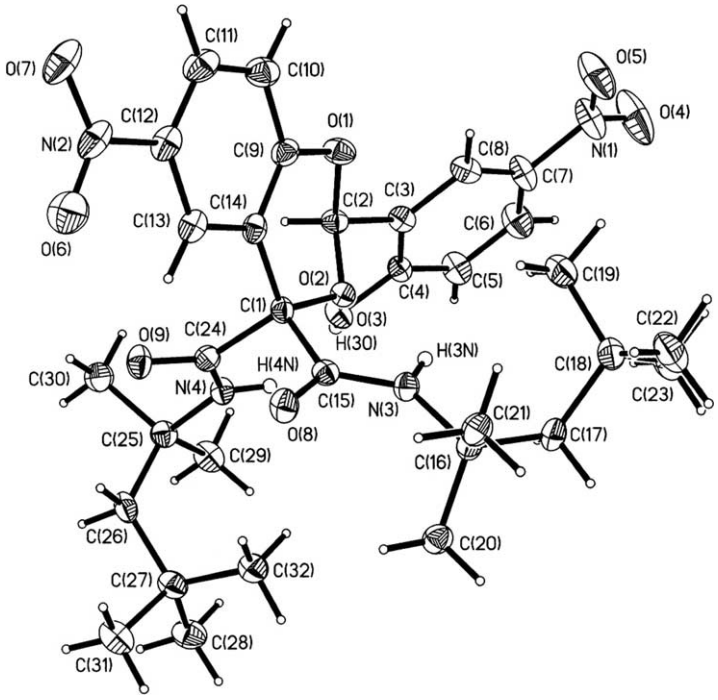
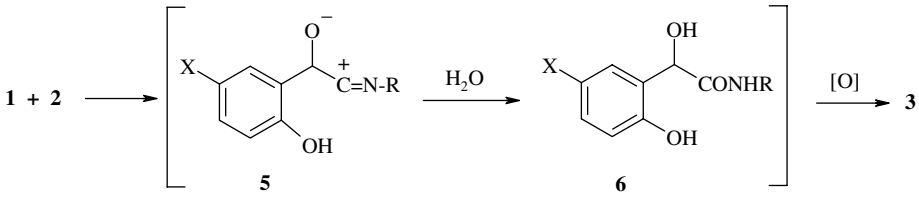
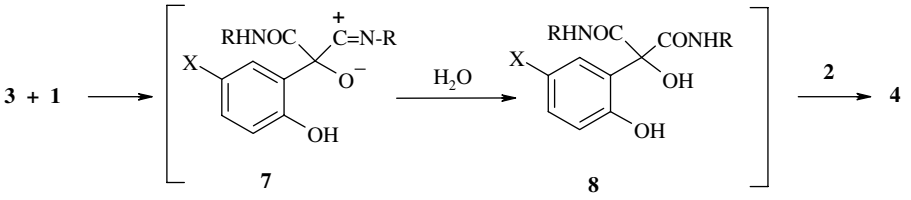


Figure 1. X-ray crystal structure (ORTEP) of **4f**. Arbitrary numbering.



Scheme 2.



Scheme 3.

A plausible mechanism for formation of **4** is proposed in Scheme 3. The reaction starts with nucleophilic attack of the isocyanide on the electron-deficient ketone group of **3** and subsequent addition of water gives adduct **8**. Then, the dihydroxy compound **8** undergoes a condensation reaction with **2** to form **4**. When compound **3f** was reacted with **1e** and **2b**, the reaction mixture was consistent with the presence of **3f** and **4f** in a 1:9 ratio. Thus, the formation of **4f** from **3f** is confirmed.

In conclusion, we have uncovered a novel reaction of alkyl isocyanides with 2-hydroxybenzaldehyde or 2-hydroxy-5-nitrobenzaldehyde to afford *N*-alkyl-2-aryl-2-oxoacetamides and N^2,N^4-dialkyl-2-aryl-4*H*-1,3-benzodioxine-2,4-dicarboxamides in nearly 1:1 ratios. Treatment of 2,6-dimethylphenyl isocyanide with 2-hydroxy-5-nitrobenzaldehyde affords only the 2-oxoacetamide derivative. The presence of the electron-withdrawing nitro group increases the rate of these reactions, while no reaction was observed when electron-donating substituents, such as methoxy were present.

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8. Typical procedure for the synthesis of *N*-(*tert*-butyl)-2-(2-hydroxyphenyl)-2-oxo-acetamide (**3a**) and N^2,N^4-di-*tert*-butyl-2-(2-hydroxyphenyl)-4*H*-1,3-benzodioxine-2,4-dicarboxamide (**4a**): To a stirred solution of 2-hydroxybenzaldehyde (0.24 g, 2 mmol) in CH_2Cl_2 (10 mL) was added dropwise at −10 °C over 10 min *tert*-butyl isocyanide (0.16 g, 2 mmol). The reaction mixture was then allowed to warm to room temperature and stand for 24 h. The solvent was removed under reduced pressure to afford a mixture of products. The products **3a** and **4a** were separated by silica gel column chromatography (Merck 230–400 mesh) using *n*-hexane–EtOAc (4:1) as eluent.
Compound **3a**: Yellow powder; yield: 0.10 g (40%), mp 83–85 °C. IR (KBr) (ν_{max}/cm^{-1}): 3238 (OH), 3040 (NH), 1695 and 1671 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.46$ (9H, s, CMe_3), 6.90 (1H, dd, $^3J_{HH} = 7.6$ and 8.1 Hz, CH), 6.99 (1H, d, $^3J_{HH} = 8.1$ Hz, CH), 7.02 (1H, br s, NH), 7.51 (1H, dd, $^3J_{HH} = 7.6$ and 8.1 Hz, CH), 8.44 (1H, d, $^3J_{HH} = 8.1$ Hz, CH), 12.01 (1H, br s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 28.3$ (CMe_3), 52.2 (CMe_3), 117.9 (C), 118.7 (CH), 119.4 (CH), 133.6 (CH), 137.9 (CH), 161.8 (C–O), 163.3 (C=O), 190.6 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 222 (M^++1, 10), 221 (M^+, 5), 122 (60), 57 (100). Anal. Calcd for $C_{12}H_{15}NO_3$ (221.3): C, 65.12; H, 6.87; N, 6.32. Found: C, 65.1; H, 6.9; N, 6.3.
Compound **3b**: Yellow powder; yield: 0.10 g (38%), mp 89–91 °C. IR (KBr) (ν_{max}/cm^{-1}): 3240 (OH), 3075 (NH), 1680 and 1675 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.21$–2.00 (10H, m, 5 CH_2), 3.87 (1H, m, CHN), 6.91 (1H, dd, $^3J_{HH} = 7.4$ and 8.4 Hz, CH), 6.97 (1H, d, $^3J_{HH} = 8.4$ Hz, CH), 7.08 (1H, br, NH), 7.52 (1H, dd, $^3J_{HH} = 7.4$ and 8.4 Hz, CH), 8.49 (1H, d, $^3J_{HH} = 8.4$ Hz, CH), 12.02 (1H, s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 24.7$ ($2CH_2$), 25.4 (CH_2),32.6 ($2CH_2$), 48.9 (CHN), 118.1 (C), 118.7 (CH), 119.5 (CH), 133.6 (CH), 138.0 (CH), 161.4 (C–O), 163.4 (C=O), 190.1 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 248 (M^++1, 30), 247 (M^+, 20), 122 (80), 83 (100), 65 (80). Anal. Calcd for $C_{14}H_{17}NO_3$ (247.2): C, 68.03; H, 6.91; N, 5.63. Found: C, 68.0; H, 6.9; N, 5.6.

Compound **3c**: Yellow powder; yield: 0.11 g (40%), mp 79–81 °C. IR (KBr) (ν_{max}/cm^{-1}): 3320 (OH), 3080 (NH), 1680 and 1667 (C=O), 1569 and 1333 (NO_2). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.50$ (9H, s, CMe_3), 7.10 (1H, d, $^3J_{HH} = 9.2$ Hz, CH), 7.41(1H, s, NH), 8.33 (1H, dd, $^3J_{HH} = 9.2$ Hz and $^4J_{HH} = 1.9$ Hz, CH), 9.27 (1H, d, $^4J_{HH} = 1.9$ Hz, CH), 13.69 (1H, s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 29.4$ (C*Me*$_3$), 52.9 (*C*Me$_3$), 118.9 (C), 120.8 (CH), 130.5 (CH), 131.7 (CH), 140.3 (C), 160.9 (C), 166.8 and 186.7 (2C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 267 (M^++1, 5), 266 (M^+,10), 166 (90), 54 (100). Anal. Calcd for $C_{12}H_{14}N_2O_5$ (266.2): C, 54.15; H, 5.34; N, 10.57. Found: C, 54.1; H, 5.3; N, 10.5.

Compound **3d**: Yellow powder; yield: 0.12 g (40%), mp 84–86 °C. IR (KBr) (ν_{max}/cm^{-1}): 3355 (OH), 3170 (NH), 1688 and 1675 (C=O), 1517 and 1331 (NO_2). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.24$–2.02 (10H, m, $5CH_2$), 3.86 (1H, m, CHN), 7.10 (1H, d, $^3J_{HH} = 9.2$ Hz, CH), 7.46 (1H, br, NH), 8.35 (1H, dd, $^3J_{HH} = 9.2$ Hz and $^4J_{HH} = 2.3$ Hz, CH), 9.32 (1H, d, $^4J_{HH} = 2.3$ Hz, CH), 13.64 (1H, s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 24.6$ ($2CH_2$), 25.2 (CH_2), 32.3 ($2CH_2$), 49.6 (CHN), 118.7 (C), 120.8 (CH), 130.4 (CH), 131.8 (CH), 140.3 (C), 160.6 (C), 166.6 (C=O), 186.4 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 293 (M^++1, 10),292 (M^+, 5), 167 (50), 166 (30), 150 (50), 120 (52), 83 (90), 55 (100). Anal. Calcd for $C_{14}H_{16}N_2O_5$ (292.3): C, 57.55; H, 5.54; N, 9.58. Found: C, 57.5; H, 5.5; N, 9.6.

Compound **3e**: Yellow powder; yield: 0.20 g (65%), mp 103–105 °C. IR (KBr) (ν_{max}/cm^{-1}): 3330 (OH), 3060 (NH), 1670 and 1666 (C=O), 1522 and 1327 (NO_2). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 4.60$ (2H, d, $^3J_{HH} = 5.7$ Hz, CH_2), 7.09 (1H, d, $^3J_{HH} = 9.2$ Hz, CH), 7.32–7.38 (6H, m, C_6H_5 and CH), 7.80 (1H, br, NH), 8.34 (1H, d, $^4J_{HH} = 1.7$ Hz, CH), 13.20 (1H, s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 44.1$ (CH_2), 118.1 (C), 120.8 (CH), 128.1 (2CH), 128.3 (CH), 129.1 (2CH), 130.4 (CH), 132.0, (CH), 135.9 (C_{ipso}), 140.4 (C), 161.3 (C), 166.9 (C=O), 186.7 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 300 (M^+, 10), 166 (45), 92 (50), 91 (100), 63 (44). Anal. Calcd for $C_{15}H_{12}N_2O_5$ (300.3): C, 60.01; H, 4.05; N, 9.35. Found: C, 60.1; H, 4.1; N, 9.3.

Compound **3f**: White crystal; yield: 0.11 g (35%), mp 144–145 °C. IR (KBr) (ν_{max}/cm^{-1}): 3415 (OH), 3200 (NH), 1685 and 1670 (C=O), 1506 and 1339 (NO_2). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 0.97$ (9H, s, CMe_3), 1.50 (6H, s, $2CH_3$), 1.63 (2H, s, CH_2), 6.87 (1H, br s, NH), 8.15–8.33 (3H, m, 3 CH), 15.42 (1H, br s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 29.2$ (2*Me*), 31.4 (C*Me*$_3$), 31.9 (*C*Me$_3$), 55.6 (CH_2), 60.5 (N–*C*Me$_2$), 114.5 (C), 121.6 (CH), 129.1 (CH), 130.2 (CH), 136.7 (C), 160.2 (C), 165.2 (C=O), 186.2 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 322 (M^+, 20), 167 (80), 57 (100). Anal. Calcd for $C_{16}H_{22}N_2O_5$ (322.3): C, 59.62; H, 6.88; N, 8.69. Found: C, 59.6; H, 6.9; N, 8.7.

Compound **3g**: White crystal; yield: 0.30 g (95%), mp 152–154 °C. IR (KBr) (ν_{max}/cm^{-1}): 3415 (OH), 3200 (NH), 1685 and 1670 (C=O), 1506 and 1339 (NO_2). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 2.29$ (6H, s, 2 Me), 7.14–7.25 (4H, m, 4 CH), 8.39 (1H, dd, $^3J_{HH} = 6.4$ Hz and $^4J_{HH} = 2.7$ Hz, CH), 8.72 (1H, br s, NH), 9.53 (1H, d, $^4J_{HH} = 2.7$ Hz, CH), 13.98 (1H, br s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 18.4$ (2*Me*), 117.9 (C), 120.5 (CH), 128.6 (2C), 128.6 (2CH), 130.6 (CH), 131.4 (C), 132.3 (CH), 135.0 (CH), 140.5 (C), 159.7 (C), 167.2 (C=O), 187.2 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 314 (M^+, 12), 299 (8), 216 (27), 215 (100), 151 (74), 139 (27), 47 (22). Anal. Calcd for $C_{16}H_{14}N_2O_5$ (314.3): C, 61.12; H, 4.51; N, 8.87. Found: C, 61.1; H, 4.5; N, 8.8.

Compound **4a**: Yellow powder; yield: 0.21 g (48%), mp 214–216 °C. IR (KBr) (ν_{max}/cm^{-1}): 3255 (OH), 3055 (NH), 1680, 1677, and 1670 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.22$ (9H, s, CMe_3), 1.41 (9H, s, CMe_3), 6.48 (1H, s, CH), 6.84 (1H, br s, NH), 6.88–7.85 (8H, m, $2C_6H_4$), 8.34 (1H, br s, NH), 9.54 (1H, s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 28.2$ (C*Me*$_3$), 28.5 (C*Me*$_3$), 51.8 (*C*Me$_3$), 52.3 (*C*Me$_3$), 79.7 (C), 95.0 (CH), 117.1 (CH), 117.9 (CH), 119.1 (CH), 120.2 (C), 120.9 (C), 122.5 (CH), 125.6 (CH), 126.5 (CH), 129.5 (CH), 131.0 (CH), 153.3 (C–O), 155.8 (C–O), 167.8 (C=O), 168.1 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 427 (M^++1, 60), 426 (M^+, 10), 227 (100), 199 (60), 122 (90), 57 (65). Anal. Calcd for $C_{24}H_{30}N_2O_5$ (426.5): C, 67.62; H, 7.13; N, 6.62. Found: C, 67.6; H, 7.2; N, 6.6.

Compound **4b**: White crystal; yield: 0.26 g (55%), mp 171–173 °C. IR (KBr) (ν_{max}/cm^{-1}): 3200 (OH), 3075 (NH), 1685, 1670, and 1666 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.25$–1.97 (20H, m, $2C_6H_{11}$), 3.54 (1H, m, CHN), 3.64 (1H, m CHN), 6.54 (1H, s, CH), 6.86 (1H, br d, $^3J_{HH} = 7.2$ Hz, NH), 6.90–7.34 (4H, m, 4 CH), 7.51 (1H, t, $^3J_{HH} = 7.5$ Hz, CH), 7.70 (1H, d, $^3J_{HH} = 7.5$ Hz, CH), 7.85 (1H, d,$^3J_{HH} = 7.8$ Hz, CH), 8.43 (1H, br d, $^3J_{HH} = 7.5$ Hz, NH), 8.49 (1H, d, $^3J_{HH} = 7.8$ Hz, CH), 9.40 (1H, s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 24.4$ (CH_2), 24.4 (CH_2), 24.6 (CH_2), 24.7 (CH_2), 25.3 (CH_2), 25.5 (CH_2), 32.3 (CH_2), 32.4 (CH_2), 32.5 (CH_2), 32.7 (CH_2), 48.8 (CHN), 49.2 (CHN), 79.4 (C), 95.1 (CH), 117.1 (CH), 118.0 (CH), 119.0 (CH), 120.0 (C), 120.8 (C), 122.6 (CH), 125.7 (CH), 126.6 (CH), 129.6 (CH), 131.0 (CH), 153.3 (C–O), 155.6 (C–O), 167.9 (C=O) 168.0 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 479 (M^++1, 50), 478 (M^+, 10), 227 (100), 121 (90), 55 (80). Anal. Calcd for $C_{28}H_{34}N_2O_5$ (478.6): C, 70.31; H, 7.21; N, 5.86. Found: C, 70.3; H, 7.2; N, 5.9.

Compound **4c**: White powder; yield: 0.28 g (55%), mp 230–232 °C. IR (KBr) (ν_{max}/cm^{-1}): 3375 (OH), 3075 (NH), 1685, 1670, and 1667 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.26$ (9H, s, C*Me*$_3$), 1.45 (9H, s, C*Me*$_3$), 6.54 (1H, s, CH), 6.66 (1H, br s, NH), 7.10 (1H, d, $^3J_{HH} = 9.0$ Hz, CH), 7.30 (1H, d, $^3J_{HH} = 9.0$ Hz, CH), 8.27–8.30 (2H, m, 2CH), 8.45 (1H, br s, NH), 8.63 (1H, d, $^4J_{HH} = 2.0$ Hz, CH), 8.86 (1H, d, $^4J_{HH} = 2.0$ Hz, CH), 10.61 (1H, s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 28.2$ (C*Me*$_3$), 28.4 (C*Me*$_3$), 52.5 (*C*Me$_3$), 53.1 (*C*Me$_3$), 79.1 (C), 94.3 (CH), 119.0 (CH), 120.1 (C), 120.4 (C), 122.6 (CH), 123.2 (CH), 125.4 (CH), 127.5 (CH), 140.5 (C), 143.1 (C), 157.4 (C–O), 161.6 (C–O), 166.3 (C=O), 166.8 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 517 (M^++1, 10), 516 (M^+, 5), 417 (10), 352 (25), 301 (100), 167 (20), 57 (90). Anal. Calcd for $C_{24}H_{28}N_4O_9$ (516.5): C, 55.80; H, 5.46; N, 10.81. Found: C, 55.8; H, 5.5; N, 10.8.

Compound **4d**: Yellow powder; yield: 0.31 g (55%), mp 208–210 °C. IR (KBr) (ν_{max}/cm^{-1}): 3355 (OH), 3085 (NH), 1680, 1676, and 1670 (C=O), 1515 and 1331 (NO_2).^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.26$-1.88 (20H, m, $2C_6H_{11}$), 3.58 (1H, m, CHN), 3.65 (1H, m, CHN), 6.59 (1H, s, CH), 6.75 (1H, br d, $^3J_{HH} = 7.9$ Hz, NH), 7.10 (1H, d, $^3J_{HH} = 9.0$ Hz, CH), 7.30 (1H, d, $^3J_{HH} = 9.0$ Hz, CH), 8.27 (2H, m, 2CH), 8.55 (1H, br d, $^3J_{HH} = 7.6$ Hz, NH), 8.62 (1H, d, $^4J_{HH} = 1.9$ Hz, CH), 8.87 (1H, d, $^4J_{HH} = 1.9$ Hz, CH), 10.48 (1H, s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 24.2$ (CH_2), 24.3 (CH_2), 24.7 (CH_2), 24.8 (CH_2), 25.2 (CH_2), 25.3 (CH_2), 32.1 (CH_2), 32.2 (CH_2), 32.3 (CH_2), 32.5 (CH_2), 49.76 (CHN), 50.0 (CHN), 78.9 (C), 94.4 (CH), 118.1 (CH), 119.0 (CH), 120.1 (C), 120.3 (C), 122.6 (CH), 123.2 (CH), 125.5 (CH), 127.5 (CH), 140.4 (C), 143.1 (C), 157.5 (C–O), 161.6 (C–O), 166.3 (C=O), 166.9 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 569 (M^++1, 10), 568 (M^+, 4), 301 (15), 167 (20), 52 (100). Anal. Calcd for $C_{28}H_{32}N_4O_9$ (568.6): C, 59.16; H, 5.67; N, 9.84. Found: C, 59.2; H, 5.8; N, 9.8.

Compound **4e**: Yellow powder; yield: 0.17 g (30%), mp 245–247 °C. IR (KBr) (ν_{max}/cm^{-1}): 3355 (OH), 3085 (NH), 1685, 1680, and 1676 (C=O), 1515 and 1331 (NO_2). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 4.55$ (2H, d, $^3J_{HH} = 5.5$ Hz, CH_2), 4.62 (2H, d, $^3J_{HH} = 5.7$ Hz, CH_2), 6.60 (1H, s, CH), 6.72 (1H, br, NH), 7.12–8.85 (16H, m, $2C_6H_5$ and $2C_6H_3$), 8.57 (1H, br, NH), 11.02 (1H, s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 44.1$ (CH_2), 44.2 (CH_2), 70.0 (C), 94.4 (CH), 120.1 (C), 120.4 (C), 120.6 (CH), 122.2 (CH), 123.2 (CH), 125.3 (CH), 127.5 (2CH), 128.1 (2CH), 128.3 (2CH), 129.2 (CH), 130.3 (2CH), 131.3 (CH), 132.1 (2CH), 134.8 (C_{ipso}), 136.0 (C_{ipso}), 140.5 (C), 143.1 (C), 157.7 (C–O), 161.7 (C–O), 166.3 (C=O), 166.8 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 584 (M^+, 10), 301 (15), 167 (20), 91 (85), 52 (90). Anal. Calcd for $C_{30}H_{24}N_4O_9$ (584.5): C, 61.65; H, 4.15; N, 9.65. Found: C, 61.6; H, 4.2; N, 9.6.

Compound **4f**: Yellow powder; yield: 0.37 g (60%), mp 224–226 °C. IR (KBr) (ν_{max}/cm^{-1}): 3355 (OH), 3185 (NH), 1685 and 1676 (C=O), 1515 and 1331 (NO_2). ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 0.76$ (9H, s, CMe_3), 1.00 (9H, s, CMe_3), 1.30 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.46 (1H, d, $^2J_{HH} = 14.5$ Hz, H of CH_2), 1.64 (1H, d, $^2J_{HH} = 14.5$ Hz, H of CH_2), 1.67 (1H, d, $^2J_{HH} = 14.5$ Hz, H of CH_2), 1.97 (1H, d, $^2J_{HH} = 15.5$ Hz, H of CH_2), 6.54 (1H, s, CH), 6.87 (1H, br s, NH), 7.10 (1H, d, $^3J_{HH} = 9.0$ Hz, CH), 7.29 (1H, d, $^3J_{HH} = 9.0$ Hz, CH), 8.28 (2H, dd, $^3J_{HH} = 9.0$ Hz and $^4J_{HH} = 2$ Hz, 2CH), 8.51 (1H, br s, NH), 8.61 (1H, d, $^4J_{HH} = 2$ Hz, CH), 8.89 (1H, d, $^4J_{HH} = 2$ Hz, CH), 10.57 (1H, s, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 28.4$ (CH_3), 28.5 (CH_3), 28.9 (CH_3), 28.9 (CH_3), 31.1 (CMe_3), 31.4 (CMe_3), 31.5 (CMe$_3$), 31.6 (CMe$_3$), 51.4 (CH_2), 51.9 (CH_2), 56.3 (C–N), 56.9 (C–N), 70.0 (C), 94.2 (CH), 118.1 (CH), 118.8 (CH), 120.1 (C), 120.1 (C), 122.4 (CH), 123.4 (CH), 125.3 (CH), 127.5 (CH), 140.4 (C), 142.9 (C), 157.4 (C–O), 161.6 (C–O), 165.60 (C=O), 166.19 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 629 (M^++1, 10), 628 (M^+, 5), 167 (30), 57 (100). Anal. Calcd for $C_{32}H_{44}N_4O_9$ (628.7): C, 61.12; H, 7.05; N, 8.95. Found: C, 61.1; H, 7.2; N, 9.0.

9. CCDC-262890 contains the supplementary crystallographic data for **4f** ($C_{32.5}H_{44.5}Cl_{1.5}N_4O_9$), $F_w = 688.40$, monoclinic, space group $P2(1)/c$, $Z = 4$, $a = 13.4828(13)$ Å, $b = 16.3386(15)$ Å, $c = 16.8146(16)$ Å, $\alpha = 90°$, $\beta = 91.129(2)°$, $\gamma = 90°$, $V = 3703.4(6)$ Å^3, $D_{calcd} = 1.235$ g/cm^3, $R = 0.0751$, $R_w = 0.1240$, $-14 \leqslant h \leqslant 14$; $-17 \leqslant k \leqslant 17$; $-18 \leqslant l \leqslant 13°$; Mo ($\lambda = 0.71073$ Å), $T = 120(2)$ K. These data can be obtained free of charge from the Cambridge Crystallography Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0)1223 336033; e-mail: deposit@ccdc.cam.ac.uk.