Traceless Solid-Phase Synthesis of Substituted Benzimidazoles *via* a Base-Cleavable Linker

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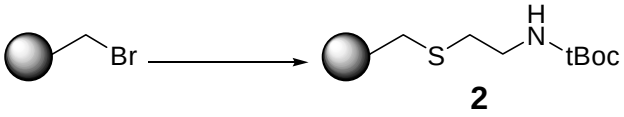
Supporting Information

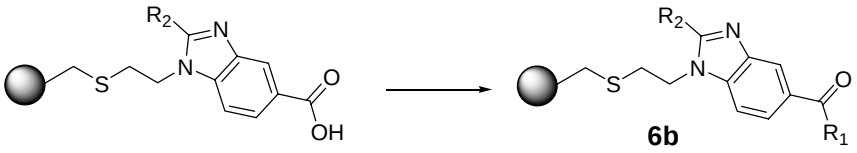
Procedures for the synthesis of resin-bound intermediates **2**, **6b**, **7** and **8**.



2

(from Scheme 1)

TentaGel-Br resin **1** (from Rapp Polmere, HL TG 12131, 40 g, 0.41 mmol/g, 16.4 mmol) was placed in a 1L peptide synthesis vessel, washed with MeOH (5 x 300 ml) then NMP (5 x 300 ml), drained and left solvated. NMP (200 ml) was added to the resin and the contents transferred to a 1L pear-shaped flask, fitted with a nitrogen-bubbler. t-Butyl-N-(2-mercaptoethyl)carbamate (Aldrich, 19.6 ml, 115 mmol, 7 eq, **Caution : Stench**) was added, followed by solid potassium carbonate (9.0 g, 66 mmol, 4 eq) and resulting resin/solution stirred with an overhead paddle-stirrer at 60°C for 12 h in a thermostatically-controlled oil bath. After this time, the slurry was transferred back to the 1L peptide synthesis vessel and the resin washed down with excess NMP. The resin was washed with vigorous nitrogen bubbling with NMP, NMP/water, MeOH/water, water, MeOH/water, NMP/water, NMP, DCM, MeOH, ether (3 x 250 ml each) and finally dried overnight *in vacuo*. A pale yellow resin was obtained (42.5 g)

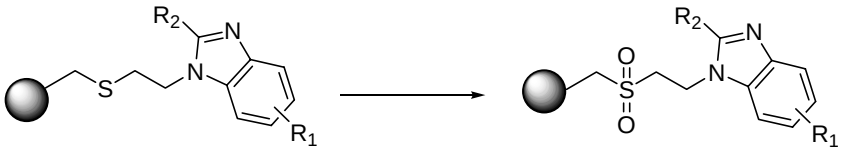


6b

(from Scheme 2)

Resin **6a**, bearing a free carboxyl group (0.57 g, 0.2 mmol. with respect to carboxyl group based on an estimated loading was 0.35 mmol.), was placed in a 20 ml glass vial and solvated with NMP (3.7 ml). Neat DECP (diethyl cyanophosphate, Fluka, 0.3 ml, 2.0 mmol., 10 equiv.) was added and the resin/solution stirred for 15 min. After

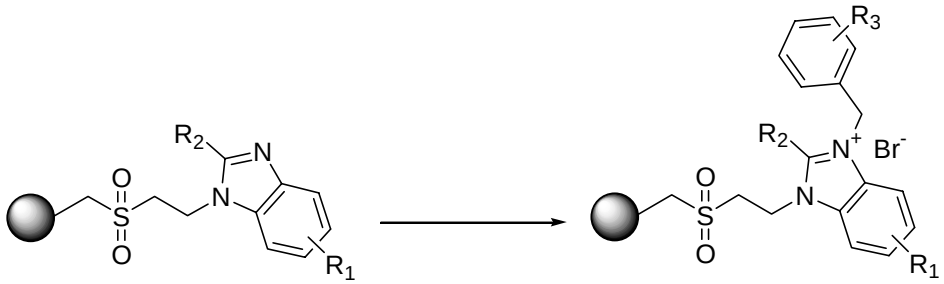
this time, a 2M solution of ethylamine in THF (Aldrich, 1.0 ml, 2.0 mmol., 10 equiv.) was added and the resin/solution stirred for 12 h at room temperature. The resins were transferred to 25 ml polypropylene filter tubes and washed with NMP, DCM, MeOH then diethyl ether (3 x 15 ml each wash) then dried overnight *in vacuo* to give resin **6b**.



7

(from Scheme 1)

Resin **6** (0.57 g, approx. 0.2 mmol with respect to sulfur) was weighed into 20 ml glass vials, then MeOH (0.5 ml) was added to each resin. A stock solution of solid Oxone (Aldrich) in water was made up (37.5 g, 61 mmol, in 150 ml water, final concentration 0.4M). Solvation of the solid in water was aided by sonication for 5 min. A portion of the aqueous Oxone solution (5 ml, 2.0 mmol, 10 eq.) was added to the vial and the resin/solution stirred for 16 h at room temperature. The resulting resin **7** was then transferred to a 25 ml polypropylene tube and washed with water, MeOH/water (1:1), MeOH, EtOH then NMP (3 x 15 ml each wash) and left solvated, prior to the subsequent step.



8

(from Scheme 1)

Resin **7**, obtained after sulfur oxidation, was left solvated in NMP and used directly in the next step. For quaternization, a benzyl or alkyl bromide (10 mmol, 50 equiv.) was dissolved in NMP and made up to 5 ml with NMP (to give a final 2M solution). This was added to resin **7** in a 20 ml glass vial and stirred at 70^{o}C for 18 h. After this time, the dark brown resin was transferred to a 25 ml polypropylene tube and washed with NMP, DCM, MeOH then finally diethyl ether (3 x 15 ml each wash) and dried overnight *in vacuo*.

Spectral comparison (^{1}H-NMR and LC) of compounds 11a/b and 12a/b

NMR spectra were obtained in DMSO-d_6 on a Varian Mercury spectrometer at 400 MHz. Chemical shifts were referenced to the residual proton resonance of DMSO-d_6 (δ 2.50). From initial inspection of the individual spectra for compound 11a and 11b from both the regular solid-phase route and the traceless solid-phase route, it was clear that compounds were identical – co-mixing the compounds and running spectra confirmed this. Below is shown;

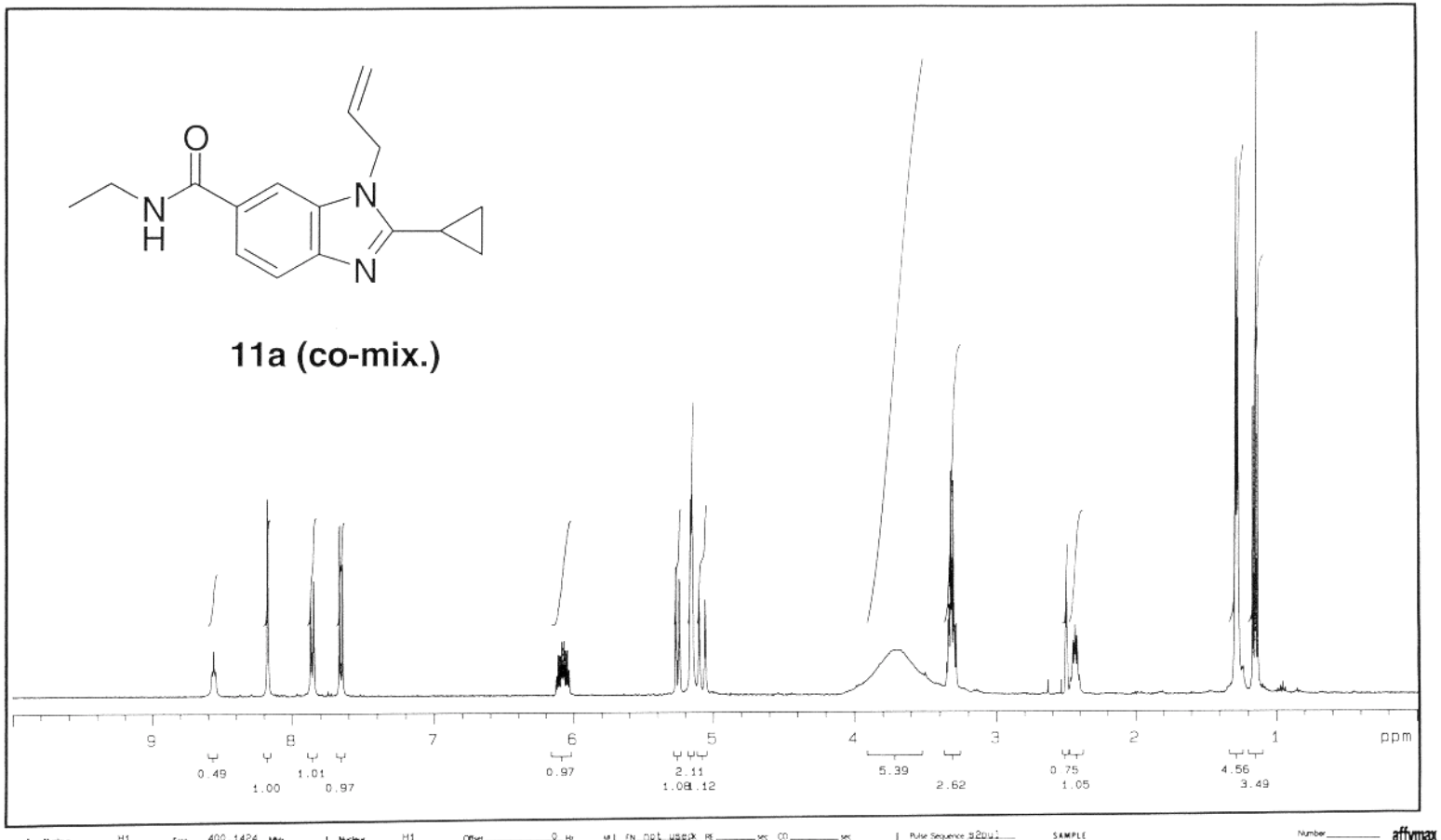
1. spectrum and chemical shifts of a mixture of 5 mg of **11a** from regular solid-phase synthetic route and 5 mg of **11a** from traceless route in 0.8 ml DMSO-d_6.
2. spectrum and chemical shifts of 10 mg of **12a** alone in 0.8 ml DMSO-d_6.
3. chemical shifts for a mixture of 5 mg of **11b** from regular solid-phase synthetic route and 5 mg of **11b** from traceless route in 0.8 ml DMSO-d_6.
4. chemical shifts for 10 mg of **12b** alone in 0.8 ml DMSO-d_6.

Compound **11a (co-mix.)**

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.27 (d, 4H), 2.44 (m, 1H), 3.32 (m, 1H), 5.08 (d, 1H, J = 17.2 Hz), 5.15 (d, 2H, J = 4.8 Hz), 5.27 (d, 1H, J = 11.4 Hz) 6.05-6.12 (m, 1H), 7.66 (d, 1H, J = 8.4 Hz), 7.86 (d, 1H, J = 8.4 Hz), 8.17 (s, 1H), 8.56 (t, 1H).

Compound **12a**

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, 3H), 1.32 (d, 4H), 2.48 (m, 1H), 3.31 (m, 1H), 5.12-5.19 (m, 3H), 5.27 (d, 1H, J = 10.2 Hz), 6.02-6.09 (m, 1H), 7.80 (d, 1H, J = 8.4 Hz), 7.92 (d, 1H, J = 8.4 Hz), 8.10 (s, 1H), 8.63 (t, 1H).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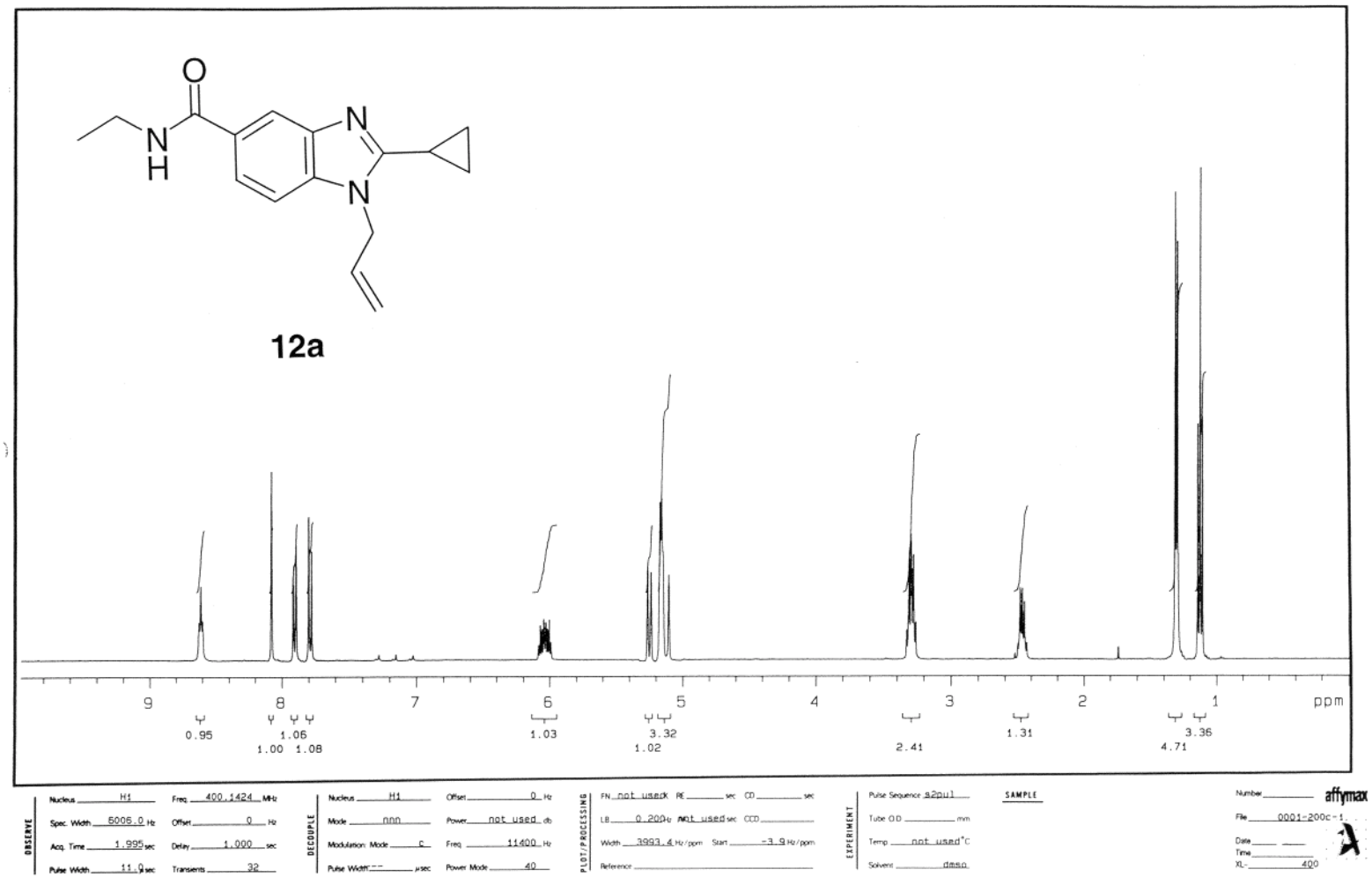
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Compounds **11b (co-mix.)**

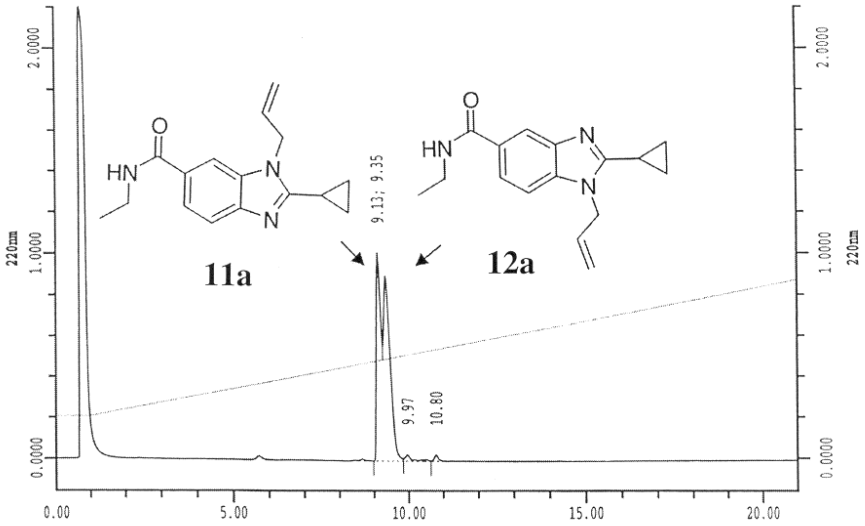
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (t, 3H), 3.34 (m, 1H), 4.95 (d, 2H), 5.00 (s, 2H), 5.26 (d, 1H), 6.10-6.17 (m, 1H), 7.61-7.64 (m, 3H), 7.78-7.83 (m, 3H), 7.88 (d, 1H, *J* = 8.4 Hz), 8.16 (s, 1H), 8.56 (t, 1H)

Compound **12b**

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (t, 3H), 3.33 (m, 1H), 4.96 (m, 3H), 5.23 (d, 1H, *J* = 10.2 Hz), 6.03-6.10 (m, 1H), 7.63 (m, 3H), 7.72 (d, 1H, *J* = 8.4 Hz), 7.80 (m, 2H) 7.91 (d, 1H, *J* = 8.4 Hz), 8.25 (s, 1H), 8.60 (t, 1H)

LC spectra

The isomers were barely separable by HPLC, but by running each individual compound, it was clear that the **11a** compounds from both routes had the same retention time, while **12a** was slightly different. From a series of co-injections, it was shown that **11a** compounds gave a single peak, and that when each was co-injected with **12a**, two peaks were obtained, as shown below. A similar pattern was observed for the **11b** compounds from each route and when either was co-injected with **12b**, again two peaks were observed. By running similar LC gradients for compounds **9a-q** and **10a-h**, the presence of a single peak was confirmed in each case.



Spectral data (^{1}H-NMR) for other compounds

Proton NMR spectra were obtained either in DMSO-d_6 on a Varian Mercury spectrometer at 400 MHz or in $CHCl_3$-*d* on a Varian Mercury spectrometer at 300 MHz. Chemical shifts were referenced either to the residual proton resonance of either DMSO-d_6 (δ 2.50) or tetramethylsilane (δ = 0.00) when using $CHCl_3$-*d*, as reported.

9a (300 MHz, $CHCl_3$-*d*) δ 0.89 (t, 3H), 1.33 (m, 5H), 1.81 (m, 3H), 2.78 (t, 2H), 5.38 (s, 2H), 7.02 (d, 2H, *J* = 8.5 Hz), 7.10 (d, 2H, *J* = 8.5 Hz), 7.17 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz), 7.62 (d, 2H), 7.74 (s, 1H).

9b (400 MHz, DMSO-d_6) δ 5.79 (s, 2H), 6.77 (d, 1H, *J* = 7.8 Hz), 7.30 (dd, 1H, *J* = 8.7 Hz, *J* = 2.0 Hz), 7.4-7.6 (m, 5H), 7.65 (dd, 2H, *J* = 7.8 Hz , *J* = 1.6 Hz), 7.83 (d, 1H), 7.86 (d, 1H, *J* = 8.7 Hz).

9c (400 MHz, DMSO-d_6) δ 5.79 (s, 2H), 7.22 (d, 2H, *J* = 8.8 Hz), 7.31 (dd, 1H, *J* = 8.8 Hz, *J* = 1.8 Hz), 7.39 (t, 1H), 7.5-7.6 (m, 5H), 8.13 (d, 2H, *J* = 8.8 Hz).

9e (300 MHz, $CHCl_3$-*d*) δ 1.25 (d, 6H), 2.95 (m, 1H), 5.44 (s, 2H), 7.0-7.1 (m, 3H), 7.16 (d, 1H), 7.25-7.35 (m, 5H), 7.60 (d, 2H), 7.81 (s, 1H).

9f (300 MHz, $CHCl_3$-*d*) δ 0.87 (t, 3H), 1.25-1.35 (m, 4H), 1.83 (m, 2H), 2.78 (t, 2H), 3.90 (s, 3H), 5.55 (s, 2H), 6.91 (dd, 1H), 7.1-7.2 (m, 3H), 7.54 (d, 1H), 7.98 (d, 2H).

9g (300 MHz, $CHCl_3$-d) δ 1.27 (s, 9H), 5.55 (s, 2H), 6.93 (m, 3H), 7.19 (d, 1H), 7.28 (d, 2H), 7.47 (m, 3H), 7.63 (d, 1H), 7.68 9d, 2H).

9h (400 MHz, DMSO-d_6) δ 2.28 (s, 3H), 5.57 (s, 2H), 6.41 (d, 2H, *J* = 7.7 Hz), 7.03-7.10 (m, 2H), 7.15 (t, 1H), 7.2-7.3 (m, 2H), 7.40 (t, 1H), 7.47 (d, 2H, *J* = 7.7 Hz), 7.5-7.6 (m, 1H), 7.61 (d, 1H, *J* = 8.1 Hz).

9j (400 MHz, DMSO-d_6) δ 1.22 (d, 6H), 2.95 (m, 1H), 5.60 (s, 2H), 6.99 (d, 2H, *J* = 7.7 Hz), 7.11 (dd, 1H, *J* = 8.1 Hz, *J* = 3.7 Hz), 7.2-7.3 (m, 4H), 7.42 (d, 2H, *J* = 8.1 Hz), 7.58 (d, 1H, *J* = 8.1 Hz), 7.64 (d, 2H, *J* = 7.7 Hz).

9k (400 MHz, DMSO-d_6) δ 0.82 (t, 3H), 1.26 (m, 4H), 1.71 (m, 2H), 2.88 (t, 2H), 3.20 (s, 3H), 5.64 (s, 2H), 7.03 (d, 2H, *J* = 8.4 Hz), 7.53 (d, 2H, *J* = 8.4 Hz), 7.75 (d, 1H, *J* = 8.4 Hz), 7.83 (d, 1H, *J* = 8.4 Hz), 8.14 (s, 1H).

9l (300 MHz, $CHCl_3$-*d*) δ 2.25 (s, 6H), 3.06 (s, 3H), 5.46 (s, 2H), 6.65 (s, 1H), 6.95 (s, 1H), 7.4-7.5 (m, 3H), 7.72 (d, 2H), 7.87 (d, 2H), 8.00 (d, 1H).

9m (300 MHz, $CHCl_3$-*d*) δ 3.08 (s, 3H), 5.33 (s, 2H), 6.58 (d, 1H), 6.74 (d, 1H), 7.4-7.5 (m, 3H), 7.72 (d, 2H), 7.87 (d, 2H), 8.00 (d, 1H).

9n (300 MHz, $CHCl_3$-*d*) δ 1.27 (d, 6H), 3.04 (s, 3H), 5.56 (s, 2H), 6.9-7.0 (m, 1H), 7.08 (d, 2H), 7.22 (dd, 2H), 7.4-7.6 (m, 4H), 7.87 (d, 1H), 7.95 (s, 1H), 8.02 (d, 1H).

9p (400 MHz, DMSO-d_6) δ 5.36 (s, 2H), 6.93 (d, 2H), 7.18-7.24 (m, 3H), 7.4-7.5 (m, 2H), 7.58-7.67 (m, 3H),7.71 (d, 1H, *J* = 8.8 Hz), 7.89 (s, 1H).

9q (300 MHz, $CHCl_3$-*d*) δ 1.26 (d, 6H), 2.95 (s, 3H), 5.42 (s, 2H), 7.0-7.2 (m, 2H), 7.3-7.4 (m, 7H), 7.59 (dd, 2H), 7.70 (d, 1H).

10f (400 MHz, DMSO-d_6) δ 1.13 (t, 3H), 3.30 (m, 2H), 5.69 (s, 2H), 7.05 (d, 2H, *J* = 7.0 Hz), 7.24-7.33 (m, 3H), 7.55-7.64 (m, 3H), 7.77 (d, 2H, *J* = 7.9 Hz), 7.84 (d, 1H, *J* = 8.4 Hz), 7.91 (d, 1H, *J* = 8.4 Hz), 8.13 (s, 1H), 8.55 (t, 1H).

10h (400 MHz, DMSO-d_6) δ 1.13 (t, 3H), 3.29 (m, 2H), 5.68 (s, 2H), 6.14 (s, 2H), 7.06 (d, 2H, *J* = 7.0 Hz), 7.11 (d, 1H, *J* = 8.1 Hz), 7.24-7.35 (m, 5H), 7.81 (d, 1H, *J* = 8.4 Hz), 7.90 (d, 1H, *J* = 8.4 Hz), 8.11 (s, 1H), 8.53 (t, 1H).