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Solid-phase synthesis of dibenzoxazepinones

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Abstract—Two novel solid-phase routes to the pharmaceutically relevant dibenzoxazepinone nucleus are described. In one, a key cyclisation step involves intramolecular phenolate displacement of an activated aryl fluoride. In the second, the tricyclic nucleus is prepared in solution prior to derivatisation on resin.

The dibenzoxazepinone ring system exhibits a range of biological activity such as antidepressant activity,[1] HIV reverse transcriptase inhibition,[2] anticonvulsant activity[3] as well as antipsychotic,[3] vasopressin[4] and dopamine D4 antagonist[5] activity. The number of published routes to these compounds is small and only one example discloses a solid-phase route.[6] The latter route describes the synthesis of a small library of 16 compounds although the opportunities for product diversification are limited by using the ring amide nitrogen as a linkage point. The use of 2-aminophenols further reduces synthetic flexibility due to limited commercial availability of such compounds.

To increase the ability to diversify products on solid-phase, an alternative strategy was investigated (Scheme 1). The commercially available formylindole resin **1**[7] was reductively aminated with *n*-propylamine in 1% acetic acid in DMF using sodium triacetoxyborohydride. This amination step represents the first point of diversity in a library synthesis based on this scheme. The resultant secondary amine **2** was acylated with 4-fluoro-3-nitrobenzoic acid in DCM using DIC. Conversion of the fluoro-compound **3** to a phenol **4** was achieved using acetic acid and cesium carbonate in DMF at 70°C. This reaction presumably proceeds through fluorine displacement by the acetate followed by hydrolysis of the resultant active ester. Nitro group reduction was achieved using tin(II) chloride in DMF buffered with 2,6-lutidine. The indolyl linkage is very acid labile and the inclusion of lutidine prevented premature product loss. The aniline **5** was reductively alkylated with 4-chlorobenzaldehyde in 1% acetic acid in DMF using sodium cyanoborohydride. This alkylation represents the second point of diversity in a library synthesis. The resultant secondary aniline **6** was then acylated with 2-fluoro-5-nitrobenzoic acid. This step required considerable optimisation. A single acylation step using a variety of coupling reagents and additives led to incomplete acylation and varying degrees of product purity. A double acylation frequently led to some bis-acylation (O and N). The optimal conditions involved a double acylation with DIC-HOBt, followed by hydrolysis of any ester formed using potassium carbonate in DMF. Cyclisation of **7** was effected using 5% DBU in DMF following the conditions outlined in ref. 1 to give the resin bound tricyclic product **8**. The synthesis was performed using 2 g resin, portions of which were cleaved after each step with the products verified by LC–MS and ^{1}H NMR. Cleavage of **8** from the resin was achieved using 5% TFA in DCM at room temperature for 30 min to give **9**. The product was isolated in 64% yield based on the original resin loading and was approximately 80% pure by HPLC (ELS detection).[8] It was envisaged that nitro reduction and derivatization of the resulting aniline would offer a third point of diversity. However, this reduction could not be adequately accomplished under a variety of conditions.

Consequently an alternative route which incorporated a third point of diversity was sought, and this involved initial construction of three dibenzoxazepinone templates in solution (Scheme 2). 3-Amino-4-hydroxybenzoic acid **10** was treated with methanolic HCl to give the methyl ester **11** which was reductively alkylated with 2,4,6-trimethoxybenzaldehyde to give the secondary amine **12**. This amine was acylated with 2-fluoro-5-nitrobenzoic acid using EDC and HOBt and although the product **13** required chromatography for

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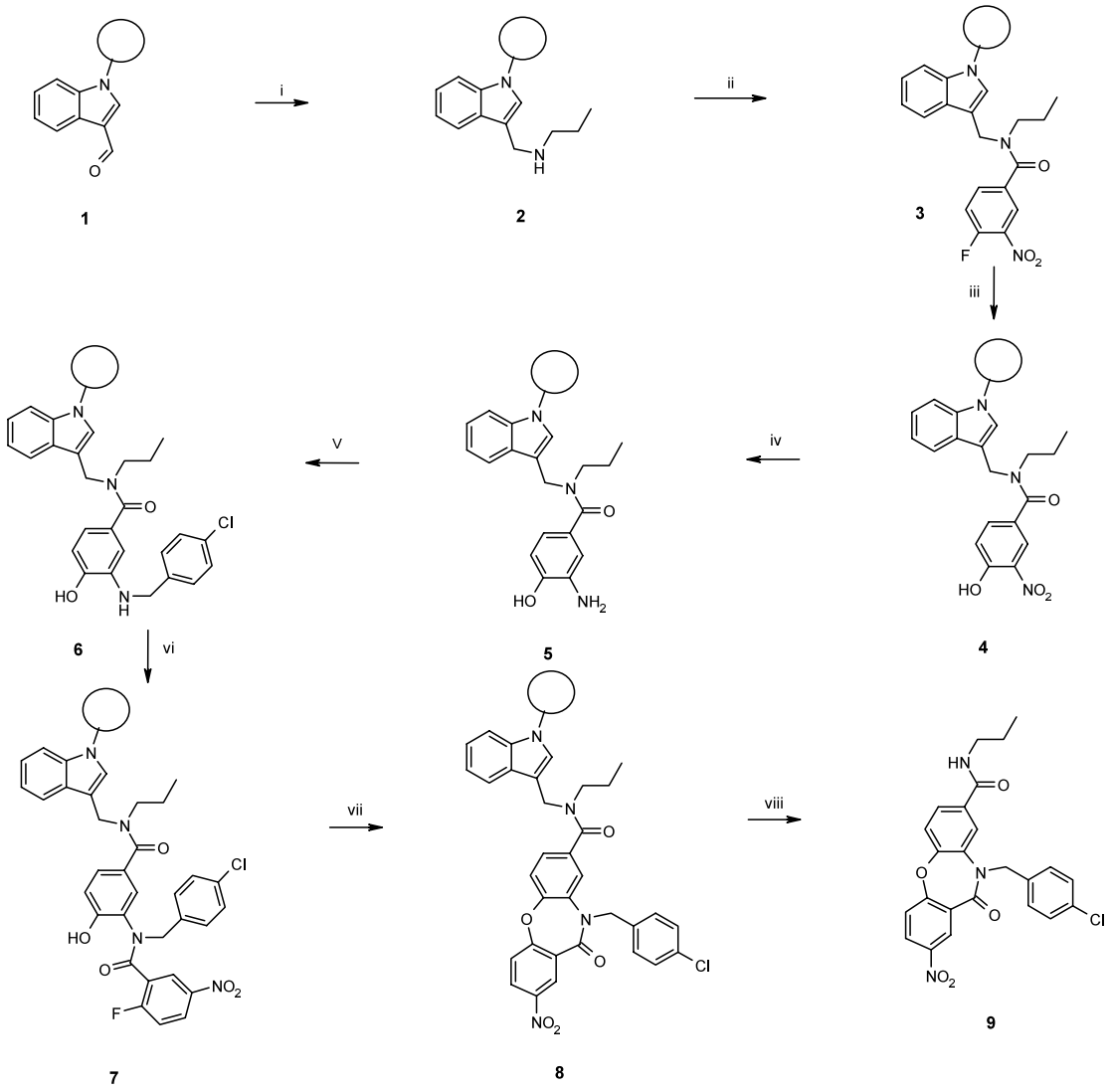
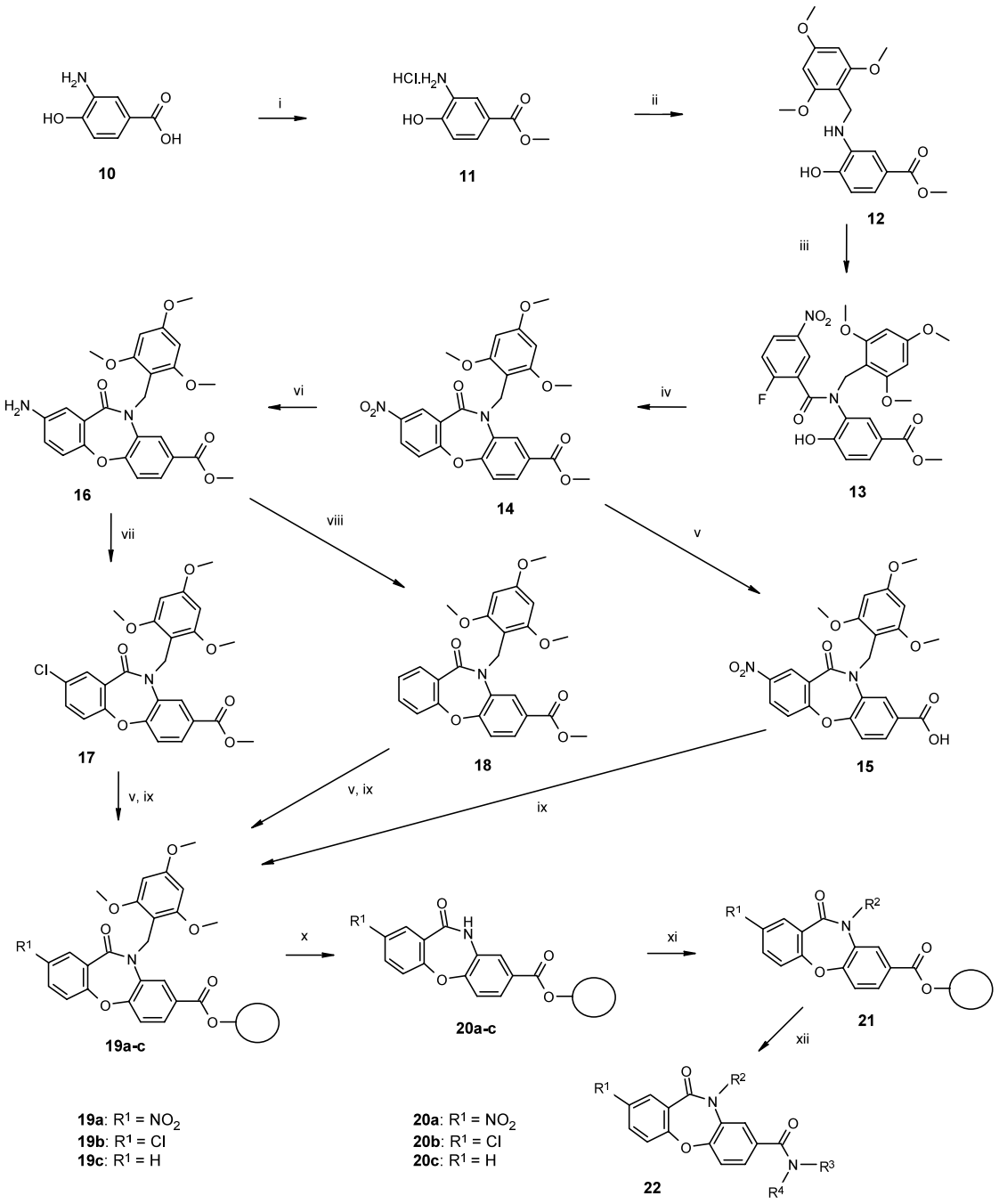


Scheme 1. *Reagents and conditions*: i, *n*-propylamine (5 equiv.), 1% AcOH in DMF, rt, 2 h then $Na(OAc)_3BH$ (3 equiv.), rt, 18 h; ii, 4-fluoro-3-nitrobenzoic acid (4 equiv.), DIC, DCM, rt, 2 h; iii, AcOH (10 equiv.), Cs_2CO_3 (10 equiv.), DMF, 70°C, 2 h; iv, $SnCl_2$ (5 equiv.), 2,6-lutidine (5 equiv.), DMF, rt, 3 h; v, 4-chlorobenzaldehyde (5 equiv.), 1% AcOH in DMF, $NaCNBH_3$ (5 equiv.), rt, 3 h; vi, 2-fluoro-5-nitrobenzoic acid (5 equiv.), HOBt, DIC, rt, 2 h, repeat, then K_2CO_3 (5 equiv.), DMF, rt, 2 h; vii, 5% DBU in DMF, rt, 18 h; viii, 5% TFA in DCM, rt, 30 min.

purification, it was found that it could instead be taken on in a crude state for cyclisation with DBU. This gave the hydrophobic tricyclic product **14** which was readily separable from impurities through chromatography.

The overall yield of **14** from **10** was 63%. Hydrogenation of **14** over Pd provided the aniline **16** which was diazotized in the presence of copper(II) chloride[9] to give chloroarene **17**. Compound **16** was also diazotised in the presence of hypophosphorous acid[10] to give the des-aminoarene **18**. The three dibenzoxazepinones were saponified and the acids (**15** and analogues) loaded onto oxime resin[11] using DIC-DMAP on a 40 g scale. The trimethoxybenzyl group of **19** was removed using 50% TFA in DCM at room temperature for 1 h to give secondary amides **20**. These were alkylated on a 2 g scale using activated alkyl halides[12] and DBU to give **21**. Alkylations under these conditions were extremely fast, exothermic and led to product loss from the resin on prolonged treatment. Optimal conditions involved cooling prior to exposure to the alkylating mixture and terminating the reaction after 5 min. Each resin combination was then cleaved with amine[13] solutions in DCM on a 100 mg scale to provide 1152 individual compounds **22**.[14] Excess amine was scavenged from solution using a macroporous anhydride resin.[15] The average crude yield was 43% based on the original resin loading with 72% of the products exhibiting greater than 70% purity by HPLC (ELS detection).



Scheme 2. *Reagents and conditions*: i, MeOH–HCl, rt, 18 h; ii, 2,4,6-trimethoxybenzaldehyde, $NaCNBH_3$, EtOH, rt, 2 h; iii, 2-fluoro-5-nitrobenzoic acid, EDC, HOBt, DMF, rt, 18 h; iv DBU, DCM, rt, 1 h; v, $LiOH_{(aq)}$, THF, MeOH, rt, 2 h; vi, H_2, Pd, THF, rt, 1 atm., 48 h; vii, *t*-butyl nitrite, $CuCl_2$, MeCN, rt, 2 h; viii, sodium nitrite, hypophosphorous acid, THF, 0°C, 30 min. then rt, 2 h, ix, oxime resin, DIC, DMAP (10%), DMF/DCM, rt, 18 h; x, 50% TFA in DCM, rt, 1 h; xi, alkyl halide (R^2X),[12] (5 equiv.), DBU (5 equiv.), DMF, 0°C to rt, 5 min; xii, amine (R^3R^4NH),[13] (5 equiv.), DCM, rt, 72 h.

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(3-formylindolyl)acetamidomethyl 1% DVB polystyrene, 1 mmol/g.

8. ^{1}H NMR (400 MHz, $CDCl_3$) 8.72 (1H, d, $J=2.5$ Hz), 8.26 (1H, dd, $J=8.9$, 2.7 Hz), 7.70 (1H, s), 7.40–7.15 (7H, m), 5.85 (1H, br s), 5.27 (2H, s), 3.34–3.23 (2H, m), 1.59–1.46 (2H, m), 0.87 (3H, t, $J=7.3$ Hz). m/z (ES+) 466 (MH^+).
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11. Novabiochem 1% DVB polystyrene, 1.3 mmol/g.
12. Alkyl halides used were methyl iodide, iodoacetonitrile, allyl bromide, bromoacetamide, methyl bromoacetate, 2-chlorobenzyl bromide, 3-chlorobenzyl bromide, 4-chlorobenzyl bromide, 2-methoxybenzyl bromide, 3-methoxybenzyl bromide, 4-methoxybenzyl bromide, 2-methylbenzyl bromide, 3-methylbenzylbromide, 4-methylbenzyl bromide, 2-fluorobenzyl bromide, 3-fluorobenzyl bromide, 4-fluorobenzyl bromide, 2-cyanobenzyl bromide, 3-cyanobenzyl bromide, 4-cyanobenzyl bromide, benzyl bromide, 2,3-difluorobenzyl bromide and 2,4-difluorobenzyl bromide. The free NH resin (**20**) was also used in step xii.
13. Amines used were ammonia, methylamine, ethanolamine, 1-amino-2-propanol, *N*-methylethylenediamine, *N*,*N*-dimethylethylenediamine, 2-methoxyethylamine, cyclopropylamine, 3-amino-1,2-propanediol, morpholine, *N*-methylpiperazine, tetrahydrofurfurylamine, *n*-propylamine, pyrrolidine, 2,2,2-trifluoroethylamine and 3-pyrrolidinol.
14. Where $R^1=NO_2$, $R^2=CH_3$, $R^3=n$-propyl, $R^4=H$, ^{1}H NMR (400 MHz, $CDCl_3$) 8.71 (1H, d, $J=2.8$ Hz), 8.25 (1H, dd, $J=8.9$, 2.6 Hz), 7.71 (1H, d, $J=1.9$ Hz), 7.40 (1H, dd, $J=8.3$, 1.8 Hz), 7.27 (1H, d, $J=8.9$ Hz), 7.24 (1H, d, $J=8.3$ Hz), 5.97 (1H, br s), 3.55 (3H, s), 3.39–3.29 (2H, m), 1.60–1.47 (2H, m), 0.92 (3H, t, $J=7.3$ Hz). m/z (ES+) 356 (MH^+).
15. Novabiochem MP-polystyrene anhydride resin, 6 mmol/g.