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Synthesis of a novel pyrrolo[1,2-*c*][1.3]benzodiazepine analogue of VPA-985

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ABSTRACT

The seven-step synthesis of a novel structural isomer of VPA-985, *N*-[3-chloro-4-(5*H*-pyrrolo[1,2-*c*][1.3]benzodiazepin-6(11*H*)-ylcarbonyl)phenyl]-5-fluoro-2-methylbenzamide, is described. (2-Aminophenyl)(1*H*-pyrrol-2-yl)methanone was converted with thiophosgene into (2-isothiocyanatophenyl)(1*H*-pyrrol-2-yl) methanone which was cyclised in the presence of base to 5-thioxo-5,6-dihydro-11*H*-pyrrolo[1,2-*c*][1.3]benzodiazepin-11-one. The latter underwent desulfurisation with Raney nickel followed by reduction with lithium aluminium hydride in the presence of aluminium trichloride and the resulting 6,11-dihydro-5*H*-pyrrolo[1,2-*c*][1.3]-benzodiazepine acylated with 2-chloro-4-nitrobenzoyl chloride to afford 6-(2-chloro-4-nitrobenzoyl)-6,11-dihydro-5*H*-pyrrolo[1,2-*c*][1.3]benzodiazepine. The nitro group in the latter compound was reduced with zinc and ammonium chloride to give the corresponding aniline derivative which was then acylated with 2-methyl-5-fluorobenzoyl chloride to provide the final product.

1. Introduction

Pyrrolobenzodiazepines have attracted the attention of synthetic chemists since the middle of the 1960s when anthramycin, a pyrrolo[2,1-*c*][1.4]benzodiazepine isolated from *Streptomyces rufuineus*, was found to possess cytostatic and antitumour properties.[1] The isolation of several related natural products, such as tomamycin, sibiromycin, neothramycins (A and B), mazethramycin, prothracarcin, DC-81, chicamycin, abbeymycin, porothramycins (A and B) and sibanomycin, from other *Streptomyces species*, led to the prolific synthesis of these compounds and their monomeric analogues.[2] Further development of this research area has been mostly in the direction of the synthesis of pyrrolobenzodiazepine conjugates,[3] dimers[3c,4] and to a much lesser extent trimers.[5] The biological importance of pyrrolo[2,1-*c*][1.4]benzodiazepines extends to compounds, such as VPA-985 (Lixivaptan) (Figure) an arginine vasopressin (AVP) antagonist. AVP is a cyclic disulfide peptide hormone, synthesised in the hypothalamus, stored and released into the blood from the posterior pituitary. The hormone exerts its actions through three well-defined G-protein mediated receptor sub-types: vascular V1a, hormone releasing V1b (also known as V3 receptor) and renal V2 receptors. The V2 receptors located in the kidneys are responsible for controlling water reabsorption. There are, however, also extrarenal V2 or V2-like receptors that are involved in vascular and clotting factor responses that may also contribute to pathophysiological states. Thus, there is potential to develop vasopressin V2 receptor antagonists for the treatment of disorders, such as congestive heart failure, hypertension, liver cirrhosis, renal disease, oedema and hyponatremia. VPA-985 is an orally active, selective, non-peptide antagonist that blocks AVP from binding to V2 receptors of the distal nephron and thus causing retention of water by the kidneys. The pioneering work on VPA-985 has been undertaken by Albright and co-workers[6] and developed by Cardiokine Inc. in the U.S.A. VPA-985 is currently undergoing phase III clinical trials that involve patients with hyponatremia including those with concomitant heart failure.

Other efforts to discover non-peptidic, orally active V2 selective antagonists for treating excessive renal reabsorption of water have been exemplified by compounds, such as mozavaptan (OPC-31260),[7] a benzazepine marketed since 2006 by Otsuka Pharmaceutical Co. in Japan for the treatment of hyponatremia and tolvaptan (OPC-41061),[8] also a benzazepine, developed by Otsuka Pharmaceuticals (U.K.) Ltd. currently in phase III clinical trials for cystic renal disease and is being filed for a licence for hyponatremia. In 2001 SR-121463A a spiroindolinone,[9] developed by Sanofi-Synthélabo, had entered phase IIa clinical trials for cardiovascular indications such as congestive heart failure and hypertension but never reached the marketplace. Pyrrolo[1,2-*c*][1.3]benzodiazepines are profoundly less common than pyrrolo[2,1-*c*][1.4]benzodiazepines. The first example of this ring system was reported by Horikawa and co-workers[10] who prepared methyl (2*Z*)-(5-oxo-1,2,3,5,6,11a-hexahydro-11*H*-pyrrolo[1,2-*c*][1.3]benzodiazepin-11-ylidene)acetate by a five step synthetic procedure. Methyl (2*E*)-3-pyrrolidin-2-ylacrylate was obtained in three steps starting from 1-*tert*-butyl 2-methyl pyrrolidine-1,2-dicarboxylate and methyl (triphenylphosphoranylidene)acetate and then coupled with

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2-iodobenzoic acid to give methyl (2*E*)-3-(1-{[(2-iodophenyl)-amino]carbonyl}pyrrolidin-2-yl)acrylate, which underwent an intramolecular Heck reaction to afford the product. The other two examples in the literature were prepared by our group.[11] Cyclisation of (2-isothiocyanatophenyl)(1*H*-pyrrol-2-yl)methanone and 2-(2-isothiocyanatobenzyl)-1*H*-pyrrole with potassium carbonate in DMF afforded 5-thioxo-5,6-dihydro-11*H*-pyrrolo[1,2-*c*][1.3]benzodiazepin-11-one and 6,11-dihydro-5*H*-pyrrolo[1,2-*c*][1.3]benzodiazepine-5-thione, respectively. Herein, we report on the synthesis of the first structural isomer of VPA-985, pyrrolo[1,2-*c*][1.3]benzodiazepine **1** (Fig. 1).

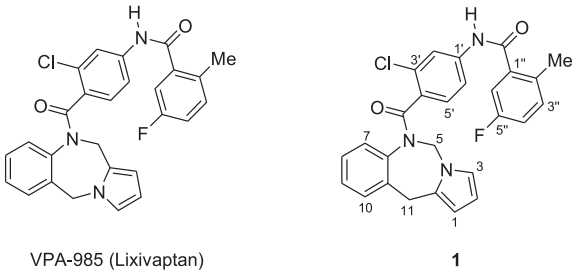
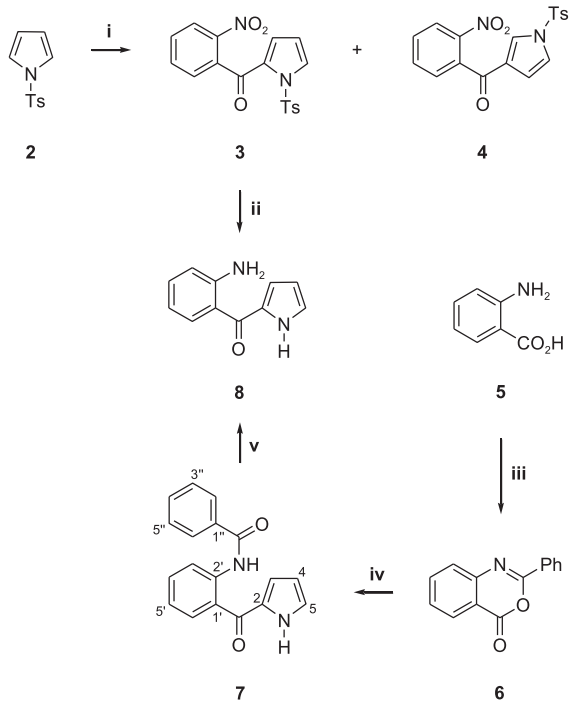


Fig. 1. Biologically active VPA-985 and analogue 1.

2. Results and discussion

The route towards **1** involves seven steps starting from (2-aminophenyl)(1*H*-pyrrol-2-yl)methanone **8** (Scheme 1). Amine **8** has been previously prepared in two steps by acylation of 1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole **2** with 2-nitrobenzoyl chloride and stannic chloride as catalyst, chromatographic separation of **3** in 56% yield from a mixture with its 3-isomer {1-[(4-methylphenyl)-sulfonyl]-1*H*-pyrrol-3-yl}(2-nitrophenyl)methanone **4** that was in 11% yield,[12] reduction of **3** to (2-aminophenyl)[1-(toluene-4-sulfonyl)-1*H*-pyrrol-2-yl](1*H*-pyrrol-2-yl)methanone by catalytic hydrogenation with 5% palladium-on-carbon in methanol and then, without isolation, detosylation by addition of aqueous sodium hydroxide and heating to give **8** in 80% overall yield.[11]

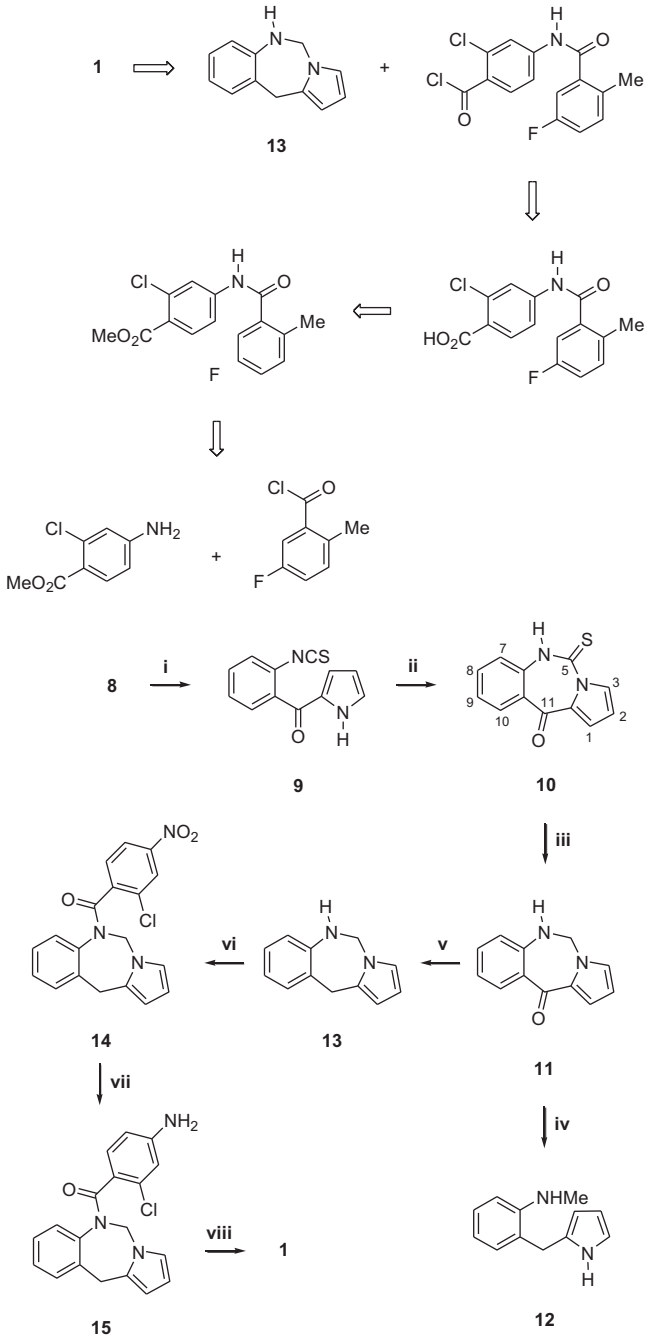


Scheme 1. Reagents and conditions: (i) 2-$NO_2C_6H_4COCl$, $ClCH_2CH_2Cl$, $SnCl_4$; **3** (56%), **4** (11%), (ii) (a) H_2, 5% Pd/C, MeOH, rt, 8 h, (b) aq 2 M NaOH, MeOH, reflux, 5 h, 80%, (iii) (a) Na_2CO_3, THF, 5 °C, (b) benzoyl chloride, THF, (c) rt 48 h, (d) H_2O 15 min, 90%, (iv) (a) EtMgBr 2.8 M in THF, pyrrole, dry toluene, 3–15 °C, (b) rt 30 min, (c) **6**, dry THF, 15 min, rt 16 h, reflux 5 h, (d) satd aq NH_4Cl, rt 30 min, 95%, (v) (a) MeOH, aq 10 M NaOH, reflux 24 h, (b) H_2O, rt 3 h, 93%.

Alternatively, amine **8** was prepared in three steps. Treatment of anthranilic acid **5** and benzoyl chloride with potassium carbonate in tetrahydrofuran afforded 2-phenyl-4*H*-3,1-benzooxazin-4-one **6**. Compound **6** was then treated with pyrrole, previously reacted with ethylmagnesium chloride, at room temperature for 24 h to afford **7** in 95% yield. Earlier, Llopard and Joule[13] reported that the same reaction stirred for 45 min and then heated under reflux for 3 h gave **7** in 81% yield. Hydrolysis of **7** by heating in methanol containing aqueous sodium hydroxide gave amine **8** in 79% overall yield, a significant improvement over the previous method.

The conversion of amine **8** to isothiocyanate **9** required reaction with thiophosgene in dry toluene in the presence of excess triethylamine (Scheme 2). Isothiocyanate **9**, obtained in 88% yield, underwent intramolecular addition of the in situ generated pyrrolyl anion to the isothiocyanate group, when treated with potassium carbonate in DMF, to afford pyrrolobenzodiazepine **10** in 90% yield. Reductive desulfurisation of thioamides to amines using Raney nickel has been widely used since it is a mild reducing agent acting with high selectivity in this reaction.[14] Therefore, compound **10** was subjected to hydrogenolysis with Raney nickel in boiling ethanol for 5 min to afford amine **11** in 66% yield. Characteristic features in the ^{1}H NMR of **10** in DMSO-d_6 are the chemical shifts at 6.65, 7.34–7.40 and 8.41–8.42 ppm corresponding to H-2, H-1 and H-3 appearing further downfield than the respective chemical shifts of **11** in $CDCl_3$ at 6.22, 6.77–6.80 and 7.20–7.26 ppm corresponding to the same protons. Furthermore, the thioamide proton of **10** appears as a broad singlet at 12.61 ppm, while the signal due to the secondary amino proton of **11** appears also as a broad singlet upfield at 5.62 ppm and the adjacent methylene group as a doublet at 5.17 ppm. Measuring the NMR of sample **11** after D_2O addition results in the disappearance of the NH signal and the appearance of a singlet in the place of the doublet at 5.17 ppm, as expected.

The next step of our synthesis involved the reduction of the carbonyl group in **11** to a methylene group. In the first attempt, sodium borohydride was used in boiling propan-2-ol that caused both reduction of the carbonyl group and ring opening of the diazepine ring to afford **12**. Further attempts to reduce **11** with sodium borohydride at lower temperature using various solvents resulted in mixtures, as evidenced by TLC. Using lithium aluminium hydride in THF at room temperature resulted in a black oily residue that produced a streak on TLC. Finally, the appropriate strength of reducing agent was found using a 1:3 mol ratio of lithium aluminium hydride to aluminium(III) chloride.[15] Reduction of **11** occurred in 40 min at room temperature using dry THF as solvent to give **13** in 65% yield. In the ^{1}H NMR spectrum of **13** in DMSO-d_6 the singlet at 4.09 ppm corresponds to protons of 11-CH_2, whereas the doublet at 5.27 ppm and triplet at 6.40 ppm correspond to protons 5-CH_2 and NH, respectively. From this point on, the synthesis of **1** can be realized by two routes (Scheme 2). The first route would require preparation of 2-chloro-4-[(5-fluoro-2-methylbenzoyl)amino]-benzoic acid from 2-chloro-4-nitrobenzoic acid and 5-fluoro-2-methylbenzoic acid. This would entail protection of the carboxylic acid group of 2-chloro-4-nitrobenzoic acid as an ester group before reducing the nitro group to an amino group, amide formation of methyl 4-amino-2-chlorobenzoate with 5-fluoro-2-methylbenzoyl chloride, deprotection to give 2-chloro-4-[(5-fluoro-2-methylbenzoyl)amino]benzoic acid, which would then be transformed into its acid chloride and reacted with **13** in order to give product **1**. The second route would require the attachment of the benzene moieties, 2-chloro-4-nitrobenzoic acid and 5-fluoro-2-methylbenzoic acid, stepwise onto **13** as depicted in Scheme 2. We chose the latter route in order to avoid the extra protection/deprotection steps. Thus, 2-chloro-4-



Scheme 2. Reagents and conditions: (i) (a) **8**, Et_3N, dry toluene, 10 °C, (b) $CSCl_2$, dry toluene, rt 1 h, 88%, (ii) K_2CO_3, dry DMF, rt 3 h, 88%, (iii) Raney nickel, absolute EtOH, reflux, 5 min, 66%, (iv) $NaBH_4$, IPA, reflux 18 h, 46%, (v) $LiAlH_4$, $AlCl_3$, dry THF, 65%, (vi) (a) Et_3N, CH_2Cl_2, 5 °C, (b) 2-chloro-4-nitrobenzoyl chloride, CH_2Cl_2, rt 30 min, 84%, (vii) Zn powder, NH_4Cl, EtOH, H_2O, rt 18 h, 98%, (viii) (a) Et_3N, CH_2Cl_2, 5 °C, (b) 5-fluoro-2-methylbenzoyl chloride, CH_2Cl_2, rt 18 h, 84%.

nitrobenzoic acid was converted into 2-chloro-4-nitrobenzoyl chloride with the use of thionyl chloride and without isolation reacted with amine **13** in the presence of triethylamine. The yield of compound **14** was optimized to 84% when 3 equiv of 2-chloro-4-nitrobenzoic acid were used. Compound **14** is unstable but can be stored for 1 week in the freezer. In the ^{1}H NMR spectrum of **14** in $CDCl_3$ the 5-CH_2 protons appear as a broad singlet at 5.91 ppm probably due to its reduced mobility conferred by the adjacent amide group.

The reduction of **14** worked best with zinc and ammonium chloride and gave amine **15** in 98% yield. In the last step towards the preparation of **1**, 5-fluoro-2-methylbenzoic acid was transformed into 5-fluoro-2-methylbenzoyl chloride by heating in thionyl chloride and without isolation reacted with **15** in dry methylene chloride containing triethylamine to afford final product **1**, in 61% yield. In the ^{1}H NMR spectrum of **1** in DMSO-d_6 the amide proton stands out as a singlet at 10.55 ppm while the 5-CH_2 protons appear as a broad singlet at 5.90 ppm. The ^{13}C NMR spectrum of **1** in DMSO-d_6 shows two carbonyl groups that coincide at 167.73 ppm, whereas the characteristic doublet at 160.89 ($J_{C\text{-}5'',\,F}$=242 Hz) is due to the C-5″ coupled to the fluorine atom. Product **1** is colourless and can be kept in the freezer for several weeks but at ambient temperature it turns dark brown within a few days.

3. Conclusion

In summary, we have described a facile seven-step synthetic route to a novel pyrrolo[1,2-*c*][1.3]benzodiazepine analogue of VPA-985 from (2-aminophenyl)(1*H*-pyrrol-2-yl)methanone. The synthetic steps involve amine to isothiocyanate transformation, intramolecular pyrrolyl anion addition to isothiocyanate leading to a thioxopyrrolobenzodiazepinone, reductive desulfurisation of thioamide to amine, reduction of ketone to methylene, amide formation by acylation of a secondary amine, reduction of nitro to amino and amide formation by acylation of a primary amine.

4. Experimental

4.1. General

Melting points were taken on a Bchi 510 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 257 spectrometer, as Nujol mulls between sodium chloride discs. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Nuclear magnetic resonance spectra were measured on Brker Avance 250 or 400 spectrometers, using tetramethylsilane as internal standard. Mass spectra were obtained by use of JEOL JMS-AX 505W (low and high resolution) and Bruker Apex III (high resolution) instruments. Analytical TLC was carried out on Fluka silica gel 60 F_{254}. Preparative flash chromatography was carried out using Merck 9385 silica gel. Solvents and reagents were used as received from the manufacturers except for dichloromethane, ethyl acetate, hexane and methanol that were purified and dried according to recommended procedures.[16]

*4.1.1. N-[2-(1H-Pyrrol-2-ylcarbonyl)phenyl]benzamide (**7**).* To a stirred solution of ethylmagnesium chloride (97.5 mL, 0.27 mol, 2.8 M in THF) in dry THF (200 mL) at 3 °C under argon was added dropwise freshly distilled pyrrole (20.68 mL, 0.30 mol) in dry toluene (20 mL) at a rate so that the temperature did not exceed 15 °C. The reaction mixture was stirred at room temperature for 30 min followed by slow addition of 2-phenyl-4*H*-3,1-benzoxazin-4-one **6**[13] (29 g, 0.13 mol) in dry THF (30 mL), left stirring for 16 h and then heated for 5 h. Ammonium chloride solution (70 mL, satd aq) was slowly added at room temperature, stirred for 30 min, Na_2SO_4 (75 g) added, stirred for 45 min and then filtered. The residue was washed with dry THF and the filtrate evaporated to dryness. The viscous oil was purified by dissolving in hot toluene, cooling and then adding 50% v/v hexane. The *title compound* **7** (35.88 g, 95%) was collected as light-green microcrystals; mp 141–142 °C (lit.[13] 185 °C); R_f (25% EtOAc/hexane) 0.34; ν_{max} (Nujol) 3320, 3272, 3136, 1659, 1616 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 6.29 (1H, d, *J* 2 Hz, *H*-4), 6.79 (1H, s, *H*-3), 7.26–7.32 (2H, m, H-5, *H*-5′), 7.50–7.65 (4H, m, *H*-4′, *H*-3″, *H*-4″, H-5″), 7.85–7.92 (3H, m, *H*-3′, *H*-2″, *H*-6″), 8.37 (1H, d, *J* 8.2 Hz, *H*-6′), 11.21 (1H, s, N*H*CO), 12.22 (1H, br s, N*H*, pyrrole); δ_C (63 MHz, DMSO-d_6) 110.84, 120.59, 122.40, 123.67, 127.28 (3C), 127.41, 128.91 (2C), 131.11, 131.19, 132.13, 132.38, 134.62,

138.20, 164.85, 184.90; *m*/*z* (EI) 290.1 (M^+, 93), 289.1 (10), 224.1 (10), 196.1 (29), 185.1 (40), 169 (47), 105 (100), 77 (88), 67 (14%); HRMS (EI): M^+, found 290.1055. $C_{18}H_{14}N_2O_2$ requires 290.1055.

*4.1.2. (2-Aminophenyl)(1H-pyrrol-2-yl)methanone (**8**).* A mixture of *N*-[2-(1*H*-pyrrol-2-ylcarbonyl)phenyl]benzamide **7** (30 g, 0.10 mol), methanol (200 mL) and aqueous 10 M NaOH (50 mL) was heated to reflux for 24 h. To the hot solution water (140 mL) was added, stirred for 3 h at room temperature, and the precipitate filtered off and washed with cold water. The residue was dried under vacuum and crystallised from toluene to give the *title compound* **8** (17.84 g, 93%) as off-white microcrystals; mp 125–126 °C; [found: C, 70.94; H, 5.40; N, 15.07. $C_{11}H_{10}N_2O$ requires C, 70.95; H, 5.41; N, 15.04%]; R_f (25% EtOAc/hexane) 0.10; ν_{max} (Nujol) 3410, 3270, 1630 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 5.55 (2H, s, NH_2), 6.30 (1H, dd, *J* 3.9, 2.6 Hz, *H*-4), 6.68–6.73 (2H, m, *H*-3′, *H*-5′), 6.84 (1H, dd, *J* 3.9, 1.4 Hz, *H*-3), 7.07 (1H, dd, *J* 2.6, 1.4 Hz, *H*-5), 7.26 (1H, ddd, *J* 8.2, 7.1, 1.8 Hz, *H*-4′), 7.85 (1H, dd, *J* 8.4, 1.8 Hz, *H*-6′), 9.89 (1H, br s, N*H*); δ_C (63 MHz, $CDCl_3$) 110.74, 116.17, 116.85, 118.96, 119.85, 124.58, 131.74, 132.07, 133.10, 149.23, 186.08; *m*/*z* (EI) 187 (100 MH^+), 169 (82), 152 (18), 92 (58), 66 (11%).

*4.1.3. (2-Isothiocyanatophenyl)(1H-pyrrol-2-yl)methanone (**9**).* To a stirred solution of (2-aminophenyl)(1*H*-pyrrol-2-yl)methanone **8** (6 g, 0.04 mol) in dry toluene (250 mL) under an atmosphere of argon was added triethylamine (7.26 mL, 0.1 mol) and the mixture cooled to 10 °C. A solution of thiophosgene (3.2 mL, 0.04 mol) in dry toluene (50 mL) was added dropwise, the reaction mixture stirred at room temperature for 1 h, poured into cold water (300 mL) and neutralised with aqueous 10% $NaHCO_3$. The organic layer was separated and evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane (80 mL) and the aqueous layer is extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent evaporated under reduced pressure to give a residue. Crystallisation from ethyl acetate gave the *title compound* **9** (6.24 g, 88%) as yellowish-brown microcrystals; mp 103–104 °C; [found: C, 63.12; H, 3.50; N, 12.31. $C_{12}H_8N_2OS$ requires C, 63.14; H, 3.53; N, 12.27%]; R_f (16.5% EtOAc/hexane) 0.21; ν_{max} (Nujol) 3280, 2120, 1620 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 6.29 (1H, dd, *J* 4.0, 2.4 Hz, *H*-4), 6.66 (1H, dd, *J* 4.0, 2.9, 1.4 Hz, *H*-3), 7.21 (1H, t, *J* 3.4 Hz, *H*-5), 7.32–7.37 (2H, m, *H*-3′, *H*-5′), 7.48 (1H, dd, *J* 9.2, 8.3, 1.5 Hz, *H*-4′), 7.61 (1H, dd, *J* 8.3, 1.5 Hz, *H*-6′), 11.00 (1H, br s, N*H*); δ_C (63 MHz, $CDCl_3$) 111.06, 120.86, 126.62, 127.24 (2C), 129.10, 129.57, 129.72, 131.26, 131.34, 135.47, 182.16; *m*/*z* (EI) 228 (100 M^+), 200 (7), 168 (44), 134 (13), 94 (47%).

*4.1.4. 5-Thioxo-5,6-dihydro-11H-pyrrolo[1,2-c][1.3]benzodiazepin-11-one (**10**).* To a stirred solution of (2-isothiocyanatophenyl)(1*H*-pyrrol-2-yl)methanone **9** (6 g, 26.28 mmol) in dry DMF (60 mL) under argon, K_2CO_3 (7.26 g, 52.56 mmol) was added and the resulting mixture was stirred at room temperature for 2.5 h. The mixture was poured into water (300 mL), neutralised with aqueous 2 M HCl, the precipitate filtered, washed with water and dried under vacuum. Crystallisation from toluene gave the *title compound* **10** (5.26 g, 88%) as pale-yellow microcrystals; mp 189 °C (dec); [found: C, 63.10; H, 3.50; N, 12.31. $C_{12}H_8N_2OS$ requires C, 63.14; H, 3.53; N, 12.27%]; R_f (25% EtOAc/hexane) 0.24; ν_{max} (Nujol) 3236, 3188, 3113, 1608 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 6.65 (1H, t, *J* 3.3 Hz, *H*-2), 7.34–7.40 (2H, m, H-1, *H*-9), 7.58 (1H, d, *J* 7.9 Hz, *H*-7), 7.67 (1H, t, *J* 7.6 Hz, *H*-8), 7.97 (1H, d, *J* 7.9 Hz, *H*-10), 8.41–8.42 (1H, m, *H*-3), 12.61 (1H, br s, N*H*); δ_C (63 MHz, DMSO-d_6) 119.36, 127.13, 128.58, 131.15, 132.10, 134.56, 138.26, 139.65, 139.98, 140.68, 180.86, 182.10; *m*/*z* (EI) 228 (100 M^+), 200 (10), 195 (2), 185 (3), 170 (10), 168 (51), 134 (15), 100 (11), 94 (35%).

*4.1.5. 5,6-Dihydro-11H-pyrrolo[1,2-c][1.3]benzodiazepin-11-one (**11**).* To a stirred solution of 5-thioxo-5,6-dihydro-11*H*-pyrrolo[1,2-*c*][1.3]benzodiazepin-11-one **10** (4 g, 17.54 mmol) in EtOH (100 mL), was added freshly prepared Raney nickel catalyst[14] (10 mL catalyst in EtOH) and the reaction mixture heated to reflux for 5 min. The hot mixture was filtered over Celite®, the filter aid washed with CH_2Cl_2 (50 mL) and the combined organic filtrates evaporated under reduced pressure to afford a residue that was purified by flash chromatography (33%, 50% ethyl acetate/hexane) to give the *title compound* **11** (2.30 g, 66%) as yellow microcrystals (ethyl acetate/hexane); mp 100.5–102.5 °C; R_f (50% EtOAc/hexane) 0.12; ν_{max} (Nujol) 3362, 1610 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 5.17 (2H, d, *J* 4.4 Hz, CH_2-5), 5.62 (1H, br s, N*H*), 6.22 (1H, s, *H*-2), 6.77–6.80 (2H, m, *H*-1, *H*-7), 6.97 (1H, t, *J* 7.4 Hz, *H*-9), 7.20–7.26 (1H, m, *H*-3), 7.32 (1H, t, *J* 7.2 Hz, *H*-8), 8.39 (1H, d, *J* 7.9 Hz, *H*-10); δ_C (63 MHz, $CDCl_3$) 60.14, 109.78, 118.90, 119.18, 120.52, 123.52, 124.72, 132.25, 133.71, 134.95, 148.87, 178.65; *m*/*z* (EI) 198 (100 M^+), 181 (41), 169 (37%); HRMS (FAB) MH^+, found 199.0871. $C_{18}H_{15}N_2O_2$ requires 199.0870.

*4.1.6. N-Methyl-2-(1H-pyrrol-2-ylmethyl)aniline (**12**).* A mixture of 5,6-dihydro-11*H*-pyrrolo[1,2-*c*][1.3]benzodiazepin-11-one **11** (70 mg, 0.35 mmol) and $NaBH_4$ (34 mg, 0.88 mmol) in propan-2-ol (7 mL) was heated to reflux for 18 h. The solvent was evaporated under reduced pressure, water (30 mL) was added to the residue and then extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The oily residue was purified by flash chromatography (11% ethyl acetate/hexane) to afford the *title compound* **12** (30 mg, 46%) as a brown oil; [found: C, 77.36; H, 7.55; N, 15.08. $C_{12}H_{14}N_2$ requires C, 77.38; H, 7.58; N, 15.04%]; R_f (50% CH_2Cl_2/hexane) 0.13; ν_{max} (Nujol) 3389, 3312 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.77 (3H, s, CH_3), 3.82 (1H, br s, N*H*CH_3), 3.86 (2H, s, CH_2), 6.02–6.03 (1H, m, *H*-3), 6.11–6.13 (1H, m, *H*-4), 6.61–6.63 (1H, m, *H*-5), 6.64 (1H, dd, *J* 8.1, 1.1 Hz, *H*-3′), 6.72 (1H, dd, *J* 7.1, 1.1 Hz, *H*-5′), 7.07 (1H, dd, *J* 7.3, 1.3 Hz, *H*-6′), 7.21 (1H, dd, *J* 7.7, 1.4 Hz, *H*-4′), 7.95 (1H, br s, N*H* pyrrole); δ_C (100 MHz, $CDCl_3$) 30.71, 30.90, 106.14, 108.35, 110.29, 117.16, 117.22, 123.29, 128.24, 129.11, 130.08, 147.55; *m*/*z* (EI) 186 (100 M^+), 171 (19), 154 (12) 144 (26), 131 (14), 118 (19), 91 (10%).

*4.1.7. 6,11-Dihydro-5H-pyrrolo[1,2-c][1.3]benzodiazepine (**13**).* To a suspension of $LiAlH_4$ (621 mg, 15.15 mmol) in dry THF (15 mL) under argon, was added a solution of $AlCl_3$ (4.05 g, 30.30 mmol) in dry THF (20 mL) and the resulting mixture stirred at room temperature for 15 min. A solution of 5,6-dihydro-11*H*-pyrrolo[1,2-*c*]-[1.3]benzodiazepin-11-one **11** (1.5 g, 7.56 mmol) in dry THF (20 mL) was added dropwise, the reaction mixture stirred at room temperature for 1 h, cooled, poured into ice-water (100 mL) and then basified with an aqueous 10% w/v solution of $NaHCO_3$ to pH 8–8.5. The mixture was extracted with CH_2Cl_2 (4×25 mL) and the combined organic extracts dried (Na_2SO_4) and evaporated under reduced pressure to give a residue, which was purified by flash chromatography (50% CH_2Cl_2/hexane) to afford the *title compound* **13** (0.90 g, 65%) as colourless microcrystals (ethyl acetate/hexane); mp 140–141 °C; R_f (50% CH_2Cl_2/hexane) 0.33; ν_{max} (Nujol) 3389 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 4.09 (2H, s, CH_2-11), 5.27 (2H, d, *J* 6.1 Hz, CH_2-5), 5.81–5.92 (1H, m, *H*-2), 5.84 (1H, t, *J* 3.0, Hz, *H*-1), 6.40 (1H, t, *J* 6.1 Hz, N*H*), 6.49–6.54 (2H, m, *H*-7, *H*-9), 6.74 (1H, dd, *J* 2.6, 1.8 Hz, *H*-3), 6.90 (1H, dd, *J* 7.6, 1.5 Hz, *H*-8), 6.95 (1H, dd, *J* 7.5, 1.5 Hz, *H*-10); δ_C (100 MHz, DMSO-d_6) 31.74, 55.89, 105.39, 105.86, 117.74 (2C), 119.03, 122.14, 127.40, 131.16, 132.81, 146.18; *m*/*z* (EI) 184 (100 M^+), 167 (21), 156 (21) 128 (8), 117 (13), 91 (11), 77 (9%); HRMS (ESI): MNa^+, found 207.0882. $C_{12}H_{12}N_2Na$ requires 207.0893.

*4.1.8. 6-(2-Chloro-4-nitrobenzoyl)-6,11-dihydro-5H-pyrrolo[1,2-c][1.3]benzodiazepine (**14**).* 2-Chloro-4-nitrobenzoic acid (2.62 g, 13.02 mmol) was heated in thionyl chloride (10 mL) for 2 h. The solvent was distilled off and to the oily residue dry CH_2Cl_2 (5 mL) was added and the solvents removed under reduced pressure. Dry

CH_2Cl_2 (5 mL) was added to the oily residue of 2-chloro-4-nitrobenzoyl chloride and kept under argon. To a stirred mixture of 11-dihydro-5*H*-pyrrolo[1,2-*c*][1.3]benzodiazepine **13** (800 mg, 4.34 mmol) and Et_3N (1.8 mL, 13.02 mmol) in dry CH_2Cl_2 (20 mL) under argon at 5 °C, was added dropwise the solution of 2-chloro-4-nitrobenzoyl chloride in CH_2Cl_2 described above. The reaction mixture was stirred for 30 min at room temperature, cooled and then a saturated aqueous solution of $NaHCO_3$ (60 mL) was added slowly. The aqueous suspension was extracted with CH_2Cl_2 (3×15 mL) and the combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered and the solvent evaporated under vacuo to afford a residue that was purified by flash chromatography (16.5% ethyl acetate/hexane) to give the *title compound* **14** (1.34 g, 84%) as colourless microcrystals (ethyl acetate hexane); mp 75–77 °C; R_f (20% EtOAc/hexane) 0.20; ν_{max} (Nujol) 1666, 1523, 1347 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 4.27 (2H, s, C*H*$_2$-11), 5.91 (2H, br s, C*H*$_2$-5), 6.07 (1H, s, *H*-2), 6.12 (1H, t, *J* 3.1 Hz, *H*-1), 6.75 (1H, t, *J* 2.5 Hz, *H*-3), 6.97–7.02 (2H, m, *H*-9, *H*-10), 7.11–7.19 (2H, m, *H*-7, *H*-6′), 7.27 (1H, d, *J* 7.5 Hz, H-7), 7.90 (1H, dd, *J* 8.4, 2.0 Hz, *H*-5′), 8.14 (1H, d, *J* 2.0 Hz, *H*-3′); δ_C (63 MHz, $CDCl_3$) 32.79, 58.84, 108.08, 108.33, 118.45, 120.88, 121.49, 124.94, 126.95, 127.19, 127.58, 128.25, 128.86, 130.13, 134.92, 139.44, 141.35, 148.05, 165.76; *m*/*z* (ESI) 390.0 (MNa^+); HRMS (ESI): MNa^+, found 390.0628. $C_{19}H_{14}ClN_3NaO_3$ requires 390.0618.

*4.1.9. 3-Chloro-4-(5H-pyrrolo[1,2-c][1.3]benzodiazepin-6(11H)-ylcarbonyl)aniline (**15**).* To a stirred solution of 6-(2-chloro-4-nitrobenzoyl)-6,11-dihydro-5*H*-pyrrolo[1,2-*c*][1.3]benzodiazepine **14** (1.0 g, 2.72 mmol) in ethanol (40 mL) was added zinc powder (3.2 g, 48.96 mmol) and an ammonium chloride solution (15 mL. 1.31 g, 24.48 mmol). The resulting mixture was stirred at room temperature for 18 h, filtered over Celite®, the filter aid washed with hot ethyl acetate (25 mL) and the combined filtrates evaporated under reduced pressure to leave an aqueous suspension to which water (90 mL) was added and then extracted with ethyl acetate (4×20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent evaporated under vacuo to afford a residue that was purified by flash chromatography (33% ethyl acetate/hexane) to give the *title compound* **15** (896 mg, 98%) as pale-yellow microcrystals (ethyl acetate/hexane); [found: C, 67.54; H, 4.74; N, 12.48. $C_{19}H_{16}ClN_3O$ requires C, 67.56; H, 4.77; N, 12.44%]; mp 182 °C (dec); R_f (50% EtOAc/hexane) 0.23; ν_{max} (Nujol) 3437, 3357, 1656 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 4.17 (2H, s, C*H*$_2$-11), 5.63 (2H, s, N*H*), 5.70 (1H, br s, C*H*$_2$-5), 5.93–5.97 (2H, m, *H*-1, *H*-2), 6.31 (1H, d, *J* 8.2 Hz, *H*-3′), 6.53 (1H, s, *H*-5′), 6.69 (1H, s, *H*-3), 6.87 (1H, d, *J* 8.2 Hz, *H*-2′), 7.11–7.19 (3H, m, *H*-8, *H*-9, *H*-10), 7.34 (1H, d, *J* 7.0 Hz, *H*-7); δ_H (63 MHz, DMSO-d_6) 31.82, 59.90, 107.30, 107.48, 111.75, 113.39, 120.00, 121.28, 127.28, 127.52, 127.86, 128.07, 129.19, 129.37, 130.95, 135.89, 141.29, 151.02, 168.07; *m*/*z* (EI) 339 (15 MHH^+), 337 (36 M^+), 183 (24), 167 (6), 156 (33), 154 (100), 128 (6), 126 (10), 99 (7), 90 (7%); HRMS (ESI): MNa^+, found 360.0843. $C_{19}H_{16}ClN_3NaO$ requires 360.0877.

*4.1.10. N-[3-Chloro-4-(5H-pyrrolo[1,2-c][1.3]benzodiazepin-6-(11H)-ylcarbonyl)phenyl]-5-fluoro-2-methylbenzamide (**1**).* 2-Methyl-5-fluorobenzoic acid (9.62 g, 6.24 mmol) was heated in thionyl chloride (10 mL) for 2 h. The solvent was distilled off and to the oily residue dry CH_2Cl_2 (5 mL) was added and the solvents removed under reduced pressure. Dry CH_2Cl_2 (5 mL) was added to the oily residue of 2-methyl-5-fluorobenzoyl chloride and kept under argon. To a stirred mixture of 3-chloro-4-(5*H*-pyrrolo[1,2-*c*][1.3]benzodiazepin-6(11*H*)-ylcarbonyl)aniline **15** (700 mg, 2.08 mmol) and Et_3N (0.87 mL, 6.24 mmol) in dry CH_2Cl_2 (20 mL) under argon at 5 °C was added dropwise the solution of 2-methyl-5-fluorobenzoyl chloride in CH_2Cl_2 described above. The reaction mixture was stirred for 18 h at room temperature, cooled and then a saturated aqueous solution of $NaHCO_3$ (60 mL) was added slowly. The aqueous suspension was extracted with CH_2Cl_2 (3×15 mL) and the combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered and the solvent evaporated under vacuo to afford a residue that was purified by flash chromatography (20% ethyl acetate/hexane) to give the *title compound* **1** (600 mg, 84%) as colourless microcrystals (ethyl acetate hexane); mp 130 °C; R_f (50% EtOAc/hexane) 0.38; ν_{max} (Nujol) 3291, 1662, 1655 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 2.30 (3H, s, 3H, C*H*$_3$), 4.26 (2H, s, C*H*$_2$-11), 5.90 (2H, br s, C*H*$_2$-5), 5.97 (1H, s, *H*-2), 6.00 (1H, s, *H*-1), 6.82 (1H, s, *H*-3), 7.04–7.46 (9H, m, *H*-7, *H*-8, *H*-9, *H*-10, *H*-5′, *H*-6′, *H*-3″, *H*-4″, *H*-6″), 7.92 (1H, s, *H*-2′), 10.55 (1H, s, N*H*); δ_H (100 MHz, DMSO-d_6) 19.44, 32.76, 59.56, 108.28, 108.32, 115.22 (d, *J* 22 Hz), 118.64 (d, *J* 20 Hz), 118.47, 120.53, 121.21, 128.04 (2C), 128.47, 129.40, 129.48, 130.44, 130.95, 131.10, 132.55, 133.48 (d, *J* 8 Hz), 136.85, 138.69 (d, *J* 6 Hz), 141.43, 141.63, 160.89 (d, *J* 242 Hz, C-5″), 167.73 (2C); δ_F (376 MHz, DMSO-d_6) −117.05 (s, 1F, F-5″); *m*/*z* (EI) 475 (31 MHH^+), 473 (78 M^+), 438 (5), 292 (34), 290 (93), 261 (4), 257 (5), 183 (93), 167 (12), 154 (11), 137 (100), 109 (32%); HRMS (ESI): MNa^+, found 496.1204. $C_{27}H_{21}FClN_3NaO_2$ requires 496.1199.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.083. These data include MOL files and InChIKeys of the most important compounds described in this article.

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