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Amido-Functionalised Prodigiosenes: Synthesis and Anticancer Properties

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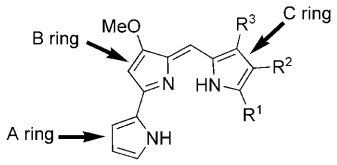

prodigiosin (**1**), R^1 =Me, R^2 =$(CH_2)_4$Me, R^3 =H
prodigiosene **2**, R^1 =R^3 =Me, R^2 =C(O)$(CH_2)_4CO_2$Me

Figure 1. Prodigiosin (**1**) and a functionalised derivative (**2**).

Prodigiosin (**1**, Figure 1)[1] is the parent member of the tripyrrolic red pigments produced by microorganisms such as *Streptomyces* and *Serratia*. This family of natural products exhibits promising anticancer, antimicrobial and immunosuppressive activities.[2–5] Published work,[2,6–9] including some from commercial ventures, demonstrates that interest in the anticancer activities of prodigiosin analogues is currently high. While biological studies on synthetic prodigiosin derivatives (prodigiosenes)[10] showed that the methoxy group in ring B is essential for anticancer activity,[11,12] fine tuning of the structure through derivatisation of the A and C rings is somewhat tolerated.[13,14] Our group has previously reported the synthesis and biological evaluation of novel C ring-functionalised prodigiosenes decorated with β-carbonyl and pendant ester functional groups,[15] which have been shown to have potent anticancer activity in vitro.[16] Importantly, a carbonyl group conjugated to the C ring facilitated isolation of the prodigiosenes, imparted stability to the tripyrrolic skeleton, and did not inherently reduce the ability of the prodigiosenes to effect copper(II)-catalysed DNA cleavage[17–19] and chloride anion transport.[20,21]

The pendant ester of **2** serves as a potential position for further manipulation, particularly for the attachment of targeting moieties.[22] In an effort to identify more potent synthetic analogues and to enhance the range of synthetically available prodigiosenes likely to be stable under physiological conditions, we investigated the facile preparation of derivatives of prodigiosene **2** (Figure 1), a compound that we have described previously.[15] Structurally, the only difference between the parent prodigiosin (**1**) and the synthetic prodigiosene **2** is the substitution pattern on the C ring: the additional methyl group, the β-carbonyl group and the pendant ester. Given the current interest in prodigiosin and its analogues, the goal of the current investigation was to develop robust methodology by which derivatives of the prodigiosene **2** could be generated. To this end, novel amido derivatives were successfully prepared, along with a prodigiosene containing a pendant ester.

Maintaining the structural core of **2**, a group of commercially available primary amines was selected in order to generate prodigiosene analogues whereby the pendant ester moiety would be replaced by amide functionality. Although indolic derivatives[2,23,24] of prodigiosin are known,[23,24] to the best of our knowledge, derivatives of prodigiosin bearing amide functionality have not been previously reported, although a singular amino-containing prodigiosene is known.[25] Although several new approaches[24–27] now complement the more traditional synthetic routes[3,5] to prodigiosenes, the methodology developed by D'Alessio[12] provides efficient access to C ring-modified prodigiosenes that can be prepared through the utilisation of Knorr-type pyrroles. Scheme 1 shows an abbreviated synthesis of **2**[15] and indicates three possible stages at which pendant amide functionality might be introduced. Strategy A: coupling of ethyl 6-(5-formyl-2,4-dimethyl-1*H*-pyrrol-3-yl)-6-oxohexanoate[15] and 4-methoxy-3-pyrrolin-2-one[28–30] gives the desired dipyrrinone skeleton of **4**, but with concurrent saponification of the ester;[15] re-esterification could potentially be replaced by formation of an amide and thus the saponification step would be necessary; the corresponding amido-containing dipyrrinone **6** could then be used in the subsequent synthesis of prodigiosenes **3a-e·HCl**. Strategy B: the fully-formed prodigiosene **2·HCl** could be derivatised through protection of the NH groups via complexation; saponification and then coupling of the resultant carboxylic acid with the amine of choice would give **3a-e·HCl**. Strategy C: if NH protection is unnecessary, direct saponification and coupling could also be exploited in the synthesis of **3a-e·HCl**. All three routes are efficient in that ethyl 6-(5-formyl-2,4-dimethyl-1*H*-pyrrol-3-yl)-6-oxohexanoate, readily available[15] through modification of a Knorr-type pyrrole, could be utilised with efficient late-stage incorporation of the amide functionality.

To investigate the feasibility of strategy A, aniline was reacted with dipyrrinone **4** in the presence of a variety of activating agents: HBTU/DMAP with an excess of aniline provided the best yield of phenyl amide **6a** (Scheme 2).[31] Subsequent triflation of the lactam in **6a** is required to synthesise the desired prodigiosene. Although a competitive reaction of the terminal amide with triflic anhydride was anticipated,[32] dipyrrinone **6a** proved to be surprisingly unreactive under our standard conditions[15] and only starting material was recovered in almost quantitative yield. More vigorous reaction conditions, such as an excess of triflic anhydride and heating at reflux, led to neither decomposition of the starting material nor significant formation of the triflate. These unexpected results indicated that this approach was not suitable for the synthesis of prodigiosenes bearing amide functionality and our efforts thus turned to strategy B.

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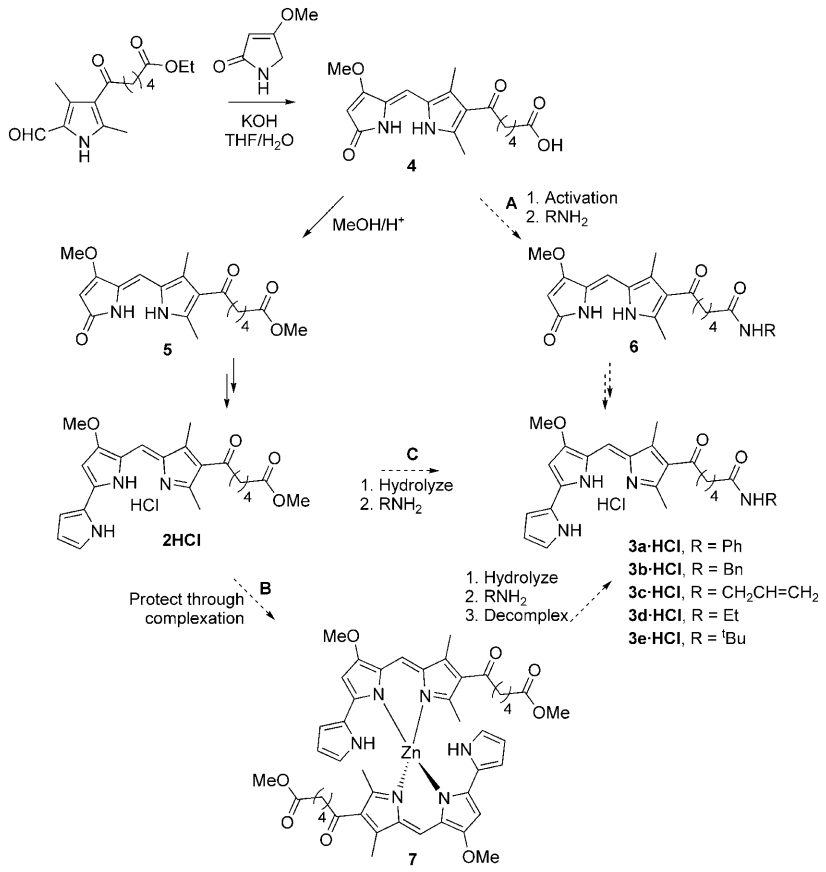
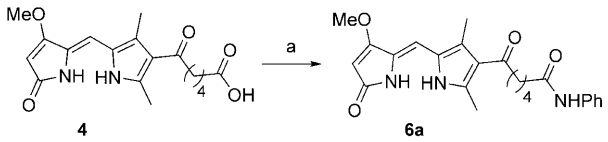


Scheme 1. Strategies for the synthesis of amido prodigiosenes.

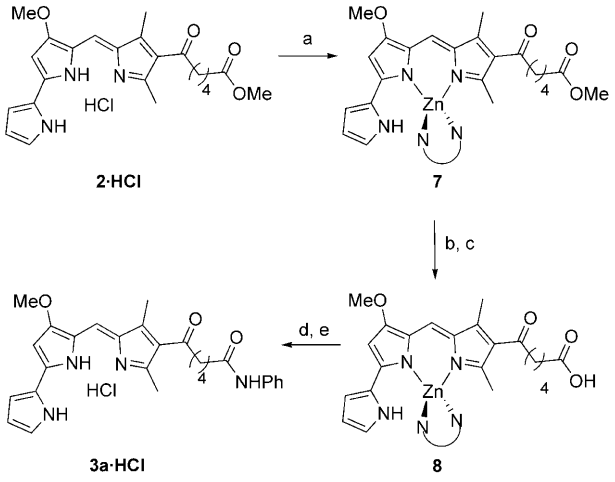


Scheme 2. Synthesis of amide **6a**. *Reagents and conditions*: a) HBTU, DMAP, $PhNH_2$, DMF, 64%.

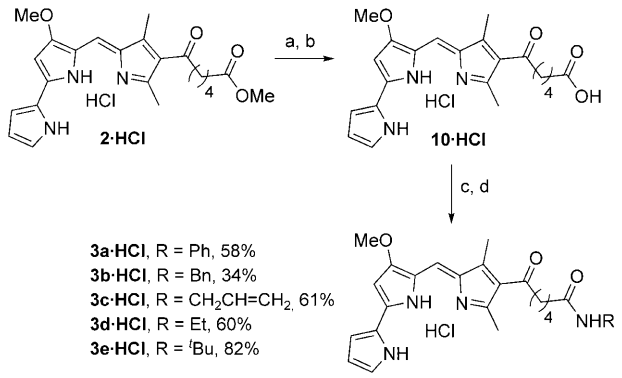
To date, little is known about the tolerance and robustness of prodigiosenes towards synthetic manipulation and little can be garnered from equivalent reactions with dipyrrins, for which only a handful of functional group interconversions have been reported.[33] To study the reactivity of prodigiosene **2**, complexation was performed to give the known dimeric prodigiosene **7**[15] (Scheme 1). This approach was modelled on the chemistry of porphyrins where most chemical transformations occur with the pyrrolic nitrogen atoms in the tetracycle complexed to a metal ion. In our case, the stabilizing template effect does not play a role, as it does with porphyrins, but possible unwanted side reactions would be prevented by complexation/protection of the ionisable NH groups in **2**. Thus, **2** was reacted with $Zn(OAc)_2$ to give the dimeric prodigiosene **7** in excellent yield (Scheme 3). Hydrolysis of the methyl ester groups in the dimeric complex was performed using aqueous KOH at reflux temperature[34] and, after acidification, **8** was isolated by filtration. Next, the peptidic bond formation was achieved by coupling the dimeric carboxylic acid **8** with aniline, again using HBTU and DMAP. Decomplexation of the resulting product by treatment with concentrated HCl led to the desired prodigiosene analogue as the hydrochloric salt **3a·HCl**.

Having accomplished the synthesis of the first example of a prodigiosene bearing a pendant amide and before following the same approach for the other desired analogues, we evaluated the efficiency of strategy C. Strategy B requires four synthetic steps to transform prodigiosene **2·HCl** into **3a·HCl**, while strategy C would only require two. In fact, hydrolysis of the methyl ester in **2** was successful under the same reaction conditions as for strategy B, giving the carboxylic acid **10·HCl** in quantitative yield (Scheme 4). This result is an improvement in relation to strategy B, where the yield for the saponification step was 69%, and indicates that NH protection is not required for the saponification of terminal esters within prodigiosenes. Subsequent activation of **10·HCl** with HBTU and DMAP followed by reaction with a variety of primary amines, gave the desired amido prodigiosenes **3a-e·HCl** in generally good yields (Scheme 4) with the overall yield of **3a·HCl** being much better than that obtained via strategy B (28% from **2·HCl** for strategy B; 58% from **2·HCl** for strategy C).

Strategy C represents a general convergent route by which to prepare prodigiosene derivatives with various pendant func-



Scheme 3. Execution of strategy B. *Reagents and conditions*: a) $Zn(OAc)_2$, NaOAc, $CHCl_3$/MeOH (1:1), 97%; b) KOH, THF/H_2O (1:1); c) HCl, 69% (2 steps); d) HBTU, DMAP, $PhNH_2$, DMSO, 60%; e) concd HCl, 46%.



Scheme 4. Execution of strategy C. *Reagents and conditions*: a) KOH, THF/H_2O (1:1); b) HCl, quant (2 steps); c) RNH_2, HBTU, DMAP, CH_2Cl_2; d) HCl, yields shown are the average of two experiments (2 steps).

tional groups: aryl, aliphatic, tertiary, and benzyl/allylic derivatives may all be prepared using this approach. To demonstrate that the scope of this approach is not confined to amines and the preparation of amides, ethanol was reacted with **10·HCl** under the same reaction conditions as for the amines, and the known ethyl ester derivative[15] was isolated in 48% yield.

Of the synthesised amido prodigiosenes, **3a·HCl**, **3b·HCl**, **3d·HCl**, and **3e·HCl** were selected by the U.S. National Cancer Institute for evaluation against 60 human cell lines derived from nine cancer cell types. The mean GI_{50}, TGI, and LC_{50} values from two five-dose screens are given in Table 1 along with the values for the lead methyl ester **2·HCl**[15] and prodigiosin itself. The amido-functionalised prodigiosenes all inhibit the growth of cancerous cells, and are all somewhat cytotoxic. However, compared to the parent methyl ester (**2·HCl**) the amido-functionalised prodigiosenes show a decrease in their average ability to both inhibit growth and kill cells in the cancer cell lines tested, rendering the amido-linkage unfavourable for future development of prodigiosene-derived anticancer agents. The evaluated prodigiosenes all show similar mean activities in the screens, indicating that the nature of the amido group does not significantly influence the anticancer effects of these compounds.

In summary, we have developed an efficient approach for the synthesis of amido-functionalised prodigiosin analogues and report the evaluation of four of these compounds against 60 human cell lines representing nine cancer cell types. The synthetic route is extremely convergent as the amino variation is introduced in the final synthetic step. This represents a breakthrough in the availability of prodigiosenes as, to our knowledge, there is only one other report of direct derivatisation of a prodigiosene, namely the formation of thio-prodigiosenes through a photoinduced redox reaction with thiol.[35] Our methodology can be extended to the coupling of amines with differing reactivity profiles, as well as to alcohols, and represents a general and useful tool for the derivatisation of prodigiosenes.

Table 1. Mean in vitro activity of prodigiosenes against 60 cancer cell lines.[a]

Compd	Log_{10} mean [GI_{50}]	Log_{10} mean [TGI]	Log_{10} mean [LC_{50}]
prodigiosin[b]	−7.85	−5.68	−6.65
2·HCl[b]	−6.19	−5.65	−5.19
3a·HCl	−5.72	−5.23	−4.73
3b·HCl	−5.59	−5.11	−4.55
3d·HCl[c]	−5.55	−5.00	−4.37
3e·HCl	−5.78	−5.28	−4.61

[a] average of two repeat screens; screening details can be found here: http://dtp.nci.nih.gov/branches/btb/ivclsp.html. [b] reported previously.[15] [c] one five-dose screen.

Experimental Section

6-[5-(4-Methoxy-1*H*,1′*H*-[2,2′]bipyrrolyl-5-ylmethylene)-2,4-dimethyl-5*H*-pyrrol-3-yl]-6-oxohexanoic acid phenyl amide hydrochloric salt (3a·HCl): Prodigiosene **10·HCl** (41 mg, 0.10 mmol) was suspended in CH_2Cl_2 (5 mL) under N_2. DMAP (22 mg, 0.02 mmol), HBTU (73 mg, 0.20 mmol), and aniline (35 μL, 0.04 mmol) were added consecutively at 0 °C. After stirring at RT for 24 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. $NaHCO_3$ solution (25 mL), 2% aq HCl solution (25 mL) and brine (25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was recrystallised from $CHCl_3$/hexanes to yield **3a·HCl** (33 mg, 69%) as a red solid: mp: 135 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.63–1.64 (4H, m), 2.32–2.35 (2H, m), 2.44 (3H, s), 2.72 (3H, s), 2.80–2.83 (2H, m), 4.08 (3H, s), 6.49 (1H, s), 6.86 (1H, s), 6.99–7.02 (1H, m), 7.11 (1H, t, J = 7.3 Hz), 7.25–7.29 (2H, m), 7.57–7.59 (3H, m), 7.66 (1H, s), 9.86 (1H, br s), 12.54 (1H, br s), 12.76 (1H, br s), 12.86 ppm (1H, br s); ^{13}C NMR (125 MHz, [D$_6$]DMSO, DEPTQ-135, one signal missing): δ = 12.6, 15.5, 23.7, 25.3, 36.9, 42.4, 60.1, 95.4, 112.3, 113.3, 119.5, 120.5, 122.3, 123.1, 123.4, 124.9, 129.1, 129.7, 137.8, 139.8, 147.9, 151.3, 167.5, 171.6, 196.8 ppm; UV/Vis ($CHCl_3$): λ_{max} (ε) = 500 (34906), 529 nm (70495); MS (ESI+): *m/z* (%): 471.24 (100) [*M*−Cl]$^+$; HRMS: [*M*−Cl]$^+$ calcd for $C_{28}H_{31}N_4O_3$: 471.2391; found 471.2394.

6-[5-(3-Methoxy-5-oxo-1,5-dihydro-pyrrol-2-ylidenemethyl)-2,4-dimethyl-1*H*-pyrrol-3-yl]-6-oxo-hexanoic acid phenylamide (6a): A suspension of dipyrrinone **4**[15] (100 mg, 0.29 mmol) in DMF (2 mL) was treated with DMAP (37 mg, 0.31 mmol), HBTU (117 mg, 0.31 mmol) and aniline (0.05 mL, 0.60 mmol) consecutively at 0 °C under N_2. The orange reaction mixture was stirred at RT for 48 h, further aniline (0.05 mL, 0.60 mmol) was then added and the reaction was stirred for a further 48 h. Finally, the reaction mixture was heated for 1 h at 60 °C under N_2 before diluting with CH_2Cl_2 (5 mL). Filtration gave the desired amide **6a** (78 mg, 64%) as a yellow solid: mp: 283 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.61–1.64 (4H, m), 2.23 (3H, s), 2.32 (2H, t, J = 6.7 Hz), 2.49 (3H, s), 2.72 (2H, t, J = 6.7 Hz), 3.86 (3H, s), 5.26 (1H, s), 6.03 (1H, s), 7.01 (1H, t, J = 7.3 Hz), 7.27 (2H, t, J = 7.9 Hz), 7.57 (2H, d, J = 7.9 Hz), 9.63 (1H, s), 9.84 (1H, s), 10.81 ppm (1H, s); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 11.6, 14.6, 23.5, 24.9, 36.4, 41.5, 58.4, 91.4, 94.4, 119.0, 121.6, 121.9, 122.9, 123.2, 125.5, 128.6, 138.0, 139.3, 166.8, 170.8, 171.1, 196.4 ppm; MS (ESI+): *m/z* (%): 420.3 (100) [*M*+H]$^+$; HRMS: [*M*+H]$^+$ calcd for $C_{24}H_{26}N_3O_4$: 420.1929; found 420.1917.

Bis[6-[5-(4-methoxy-1*H*,1′*H*-[2,2′]bipyrrolyl-5-ylmethylene)-2,4-dimethyl-5*H*-pyrrol-3-yl]-6-oxohexanoic acid] zinc(II) (8): Prodigiosene **7**[15] (49 mg, 0.06 mmol) was dissolved in THF (6 mL) under N_2. The solution was treated with aq KOH (6 mL, 5 M) and the reaction mixture was stirred at 70 °C for 24 h under N_2. The reaction was then cooled to RT, the THF was removed in vacuo and the aq solution was adjusted to pH 2 with concd HCl. The precipitate was iso-

lated by filtration, washed with H_2O and hexanes and dried in vacuo to give the desired compound **8** (32 mg, 69%) as a dark red solid: mp: 175 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.44–1.57 (8H, m), 1.94 (6H, s), 2.10–2.23 (4H, m), 2.40 (6H, s), 2.55–2.68 (4H, m), 3.96 (6H, s), 5.87 (2H, s), 6.49–6.52 (4H, m), 6.89 (2H, s), 7.21 (2H, s), 11.49 (2H, br s), 11.95 ppm (2H, br s); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 12.6, 16.9, 23.3, 24.2, 33.7, 41.4, 58.5, 95.4, 109.9, 110.6, 116.9, 123.1, 125.8, 126.1, 131.5, 132.9, 136.6, 153.6, 155.2, 166.6, 174.4, 196.1 ppm; MS (ESI−): *m/z* (%): 851 (100) $[M-H]^-$; HRMS: $[M-H]^-$ calcd for $C_{44}H_{47}N_6O_8Zn$: 851.2752; found 851.2700.

Bis[6-[5-(4-methoxy-1*H*,1′*H*-[2,2′]bipyrrolyl-5-ylmethylene)-2,4-dimethyl-5*H*-pyrrol-3-yl]-6-oxohexanoic acid phenyl amide] zinc (II) (9): A solution of **8** (13 mg, 0.02 mmol) in DMSO (0.8 mL) under N_2 was treated consecutively at RT with DMAP (4 mg, 0.03 mmol), HBTU (12 mg, 0.03 mmol) and aniline (5.5 μL, 0.06 mmol). The reaction mixture was stirred under N_2 at RT for 3 days. CH_2Cl_2 (5 mL) was added to the suspension, and the organic phase was washed with sat. $NaHCO_3$ solution (5 mL), 2% aq. HCl solution (5 mL), H_2O (5 mL) and brine (5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. After filtration over an alox pad (CH_2Cl_2/MeOH, 0→1%) and recrystallisation from $CHCl_3$/hexanes, the desired amide **9** (9 mg, 60%) was obtained as a red solid: mp: 120 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.70–1.74 (8H, m), 2.18 (6H, s), 2.36–2.38 (4H, m), 2.55 (6H, s), 2.75–2.76 (4H, m), 3.99 (6H, s), 6.07 (2H, s), 6.11 (2H, s), 6.52 (2H, s), 6.63 (2H, s), 7.05–7.07 (4H, m), 7.29–7.31 (2H, m), 7.36 (2H, s), 7.62 (4H, d, *J* = 7.8 Hz), 8.23 (2H, s), 9.25 ppm (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.3, 18.2, 23.5, 25.3, 37.6, 42.1, 58.6, 96.2, 110.9, 114.6, 117.9, 120.0, 123.3, 124.0, 126.5, 126.8, 129.0, 132.2, 133.2, 138.6, 138.7, 155.9 (2C), 167.2, 171.4, 197.8 ppm; MS (ESI−): *m/z* (%): 1001.3 (100) $[M-H]^-$; HRMS: $[M-H]^-$ calcd for $C_{56}H_{57}N_8O_6Zn$: 1001.3698; found 1001.3662.

6-[5-(4-Methoxy-1*H*,1′*H*-[2,2′]bipyrrolyl-5-ylmethylene)-2,4-dimethyl-5*H*-pyrrol-3-yl]-6-oxohexanoic acid] hydrochloric salt (10·HCl): A solution of prodigiosene **2·HCl**[15] (70 mg, 0.17 mmol) in THF (17 mL) under N_2 was treated with aq. KOH (17 mL, 5 M) and stirred at 70 °C under N_2 for 24 h. The reaction was then cooled to RT, the THF was removed in vacuo and the aq solution was adjusted to pH 2 with concd HCl. The precipitate was isolated by filtration, washed with H_2O and hexanes and dried in vacuo to give the desired prodigiosene **10·HCl** (73 mg, 99%) as a dark red solid: mp: 140 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.49–1.61 (4H, m), 2.23–2.24 (2H, m), 2.42 (3H, s), 2.71 (3H, s), 2.77–2.78 (2H, m), 4.06 (3H, s), 6.49 (1H, s), 6.85 (1H, s), 7.11 (1H, s), 7.56 (1H, s), 7.68 (1H, s), 12.03 (1H, br s), 12.56 (1H, br s), 12.80 (1H, br s), 12.89 ppm (1H, br s); ^{13}C NMR: Due to the low solubility properties of **10·HCl** no data was obtained; MS (ESI+): *m/z* (%): 396.4 (100) $[M-Cl]^+$; HRMS: $[M-Cl]^+$ calcd for $C_{22}H_{26}N_3O_4$: 396.1918; found 396.1909.

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Keywords: amides · antitumor agents · hydrolysis · natural products · prodigiosin

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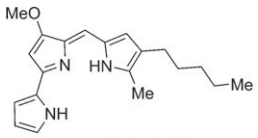
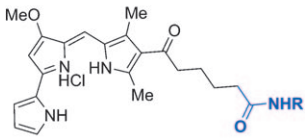
COMMUNICATIONS

Prodigiosin: Amido-functionalised prodigiosin-derived compounds were synthesised via a robust and efficient synthetic route. These compounds were then evaluated against 60 human cell lines consisting of nine diverse tumour cell types and their anticancer activities were assessed.



prodigiosin (**1**)



amido-prodigiosenes

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Amido-Functionalised Prodigiosenes: Synthesis and Anticancer Properties

