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Synthesis and antimalarial activity of prodigiosenes†

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Several analogues of the natural compound prodigiosin with modified A- and C-rings were synthesised as were some of their tin, cobalt, boron and zinc complexes. The antimalarial activity of these prodigiosenes was evaluated *in vitro* using the 3D7 *Plasmodium falciparum* strain. The presence of a nitrogen atom in the A-ring is needed for antimalarial activity but the presence of an alkyl group at the β′-position of the C-ring seems detrimental. Dibutyl tin complexes exhibit IC_{50} values mostly in the nanomolar range with equal or improved activity compared to the free-base prodigiosene ligand, despite the fact that the general toxicity of such tin complexes is demonstrably lower than that of the free-bases.

Introduction

Malaria is an infectious disease caused by a parasite (*Plasmodium*) that occurs in tropical and subtropical regions. It is responsible for more than 750 000 annual deaths and 225 million infections.[1] Although there is significant promise for future vaccines,[2] the only current course of action to prevent infection from the bite of a parasite-carrying mosquito is the use of prophylaxis and/or personal protection.[3] Moreover the emergence of drug-resistant forms of the parasite toward antimalarial drugs is an ever-burdening public health threat, and it curbs the likelihood of eradicating the disease. Chloroquine, widely used during the 1950s, is now almost ineffective and is administered in only a few countries in Central America and central Asia.[4] More worrisome is that resistance to artemisinin, the current first-line treatment against severe malaria, has emerged.[5] Although much effort has been directed towards the discovery of new antimalarial drugs,[6] the efficacy and safety of the artemisinins remains difficult to reach.[7]

Prodigiosins (Fig. 1, **1–4**) constitute a class of natural products isolated from bacterial strains such as *Serratia marcescens*.[8] These tripyrrolic red pigments have been widely studied due to their notable biological activity, including antibacterial,[9] immunosuppressive[10] and anticancer[11] properties. Although the antimalarial activity of natural prodigiosins was reported several years ago,[12] the parasiticidal activity of analogues of the prodigiosin family (termed prodigiosenes)[13] was reported only recently, with encouraging results.[14] We herein report the antimalarial activity of prodigiosenes bearing modi-

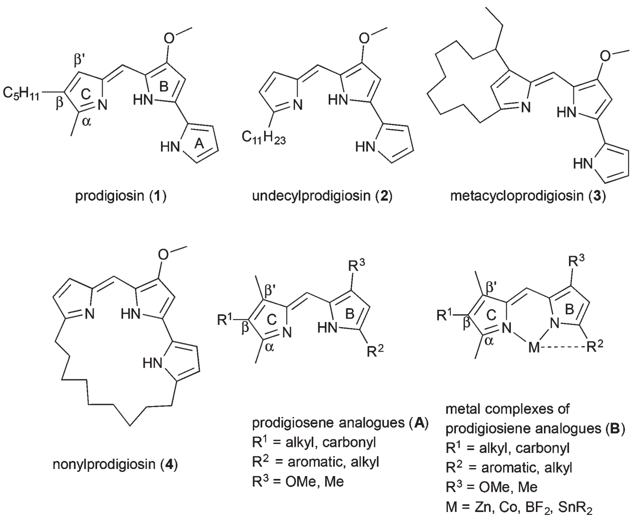

Fig. 1 Selected examples of natural prodigiosins (**1–4**) and prodigiosene analogues (**A** and **B**).

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fications at the A- and C-rings (Fig. 1, **A**), so as to begin to probe a structural activity relationship (SAR) as well as the minimal active pharmacophore. The modified C-ring features: (i) an extra methyl group at the β′-position allowing facile synthetic access *via* Knorr-type pyrroles; and (ii) an alkyl or carbonyl group at the β-position. The importance of the A-ring pyrrole in the antimalarial activity is assessed *via* substitution with other aromatic and non-aromatic groups.

Some organometallic complexes exhibit noteworthy antimalarial properties.[6c] For example, ferroquine is a ferrocenyl complex of chloroquine[15] that was evaluated in a phase II clinical trial.[16] Given this, plus the fact that tin-complexes of prodigiosenes previously demonstrated low toxicity profiles,[9g] we also report the synthesis and the first antimalarial evaluation of some metal complexes of prodigiosenes (Fig. 1, **B**) and discuss their complementary behaviour compared to the corresponding free-base dipyrrins.

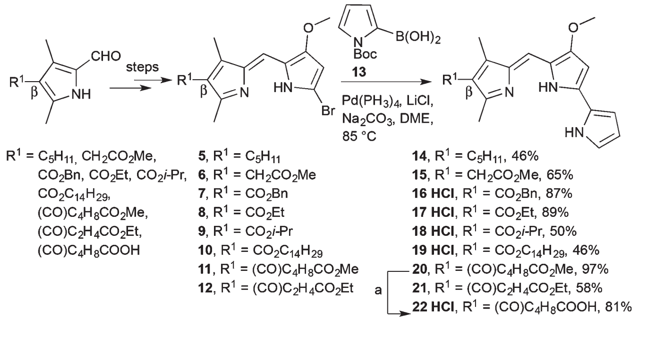
Results and discussion

Synthesis of prodigiosenes

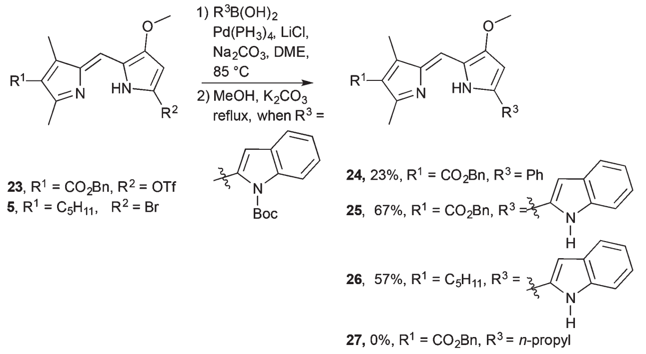
Synthesis of prodigiosenes with an A-ring pyrrole. Prodigiosenes were obtained starting from the corresponding formyl pyrroles (Scheme 1),[17] to give compounds with alkyl (**14**, **15**), carboxy (**16–19**) and acyl groups (**20–21**) at the β-position of the C-ring.

Synthesis of A-ring modified prodigiosenes and dipyrrins. A-ring modified prodigiosenes were prepared by taking advantage of the Pd-catalysed coupling, as the last step, to enable the incorporation of a range of A-ring motifs. Thus, dipyrrins **23** and **5** were subjected to Suzuki–Miyaura reaction conditions using various boronic acids (Scheme 2).

The coupling was successful when an aromatic boronic acid was used and it provided prodigiosenes **24–26** substituted with a phenyl or an indolyl A-ring. However, the Boc protecting group on the indolyl A-ring proved to be more stable to the reaction conditions than was a similarly protected pyrrolyl substituent, as the latter is usually deprotected *in situ*. Thus, an extra deprotection step using potassium carbonate in methanol was necessary in order to obtain compounds **25** and **26**. Unfortunately, when *n*-propyl boronic acid was used, the expected product (**27**) was not obtained even when employing reaction conditions that had been successful in coupling alkyl boronic acids and halogeno-arenes.[18]



Scheme 1 Synthesis of prodigiosenes **14–22**. [a]KOH, THF–H_2O, 70 °C, then HCl.

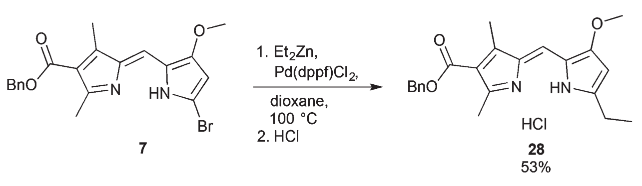


Scheme 2 Synthesis of A-ring modified prodigiosenes using a Suzuki–Miyaura coupling.

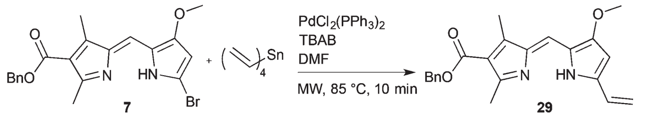
We thus moved to a Negishi-type reaction[19] in order to obtain a prodigiosene substituted with an alkyl group in lieu of an A-ring heterocycle: the ethyl-substituted dipyrrin salt **28** was rendered in 53% yield, after quenching with HCl and a simple precipitation from methanol (Scheme 3).

To extend the conjugation of the dipyrrin core we attempted a Stille coupling of tetravinyltin and dipyrrin **7** (Scheme 4).[20] The reaction was performed under microwave-promoted conditions at 85 °C for 10 min, after which time the starting material (**7**) was completely consumed. However, the extra conjugation seemed to bring instability to the system as the free-base dipyrrin **29** decomposed within a few days. Attempts to form the HCl salt of **29**, usually a stabilisation strategy for dipyrrins, also failed.

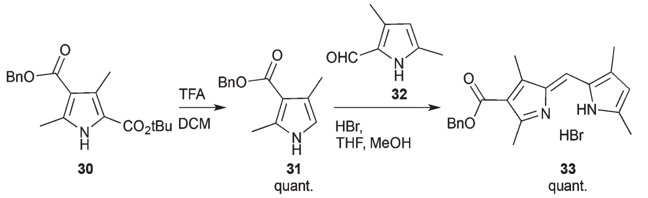
An analogue of dipyrrin **28** (Scheme 3), without the B-ring methoxy substituent and bearing a methyl group in place of the ethyl substituent, was also prepared (Scheme 5, **33**). This was obtained *via* deprotection and decarboxylation of pyrrole **30**[17a] to quantitatively give the α-free pyrrole **31**. Then, condensation with aldehyde **32**[21] gave the dipyrrin **33** in excellent yield.



Scheme 3 Synthesis of a dipyrrin substituted with an alkyl group.



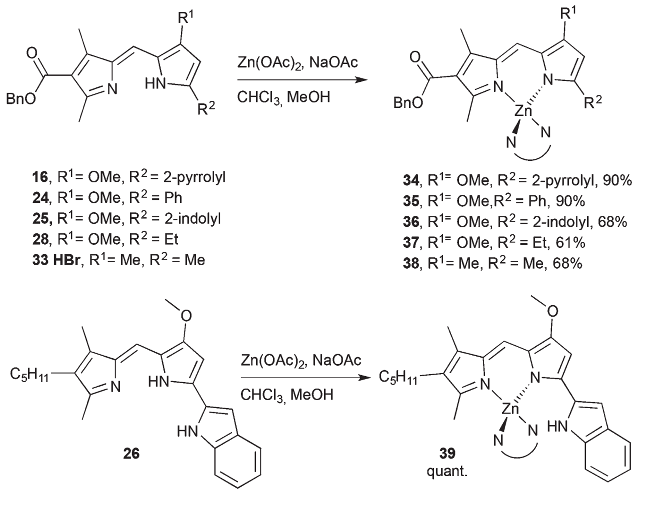
Scheme 4 Attempted synthesis of a dipyrrin substituted with an allyl group.



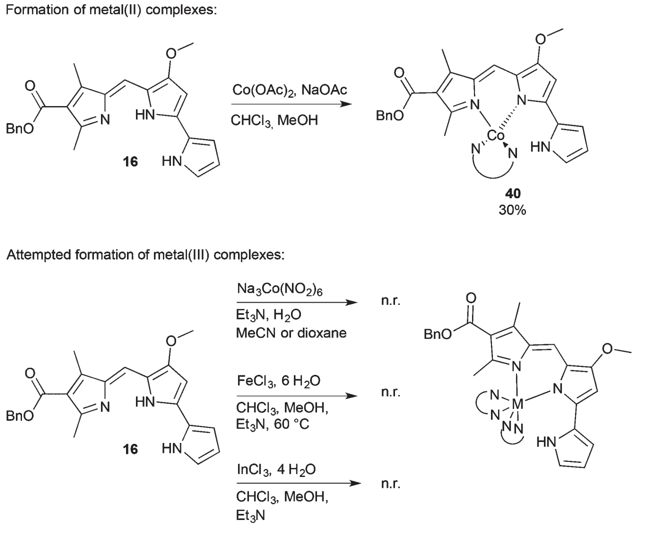
Scheme 5 Synthesis of dipyrrin **27**.

Synthesis of metal complexes of prodigiosenes and dipyrrins. Incorporation of metals into the backbone of known antimalarial drugs has provided promising results in terms of activity and toxicity.[6c] Consequently we explored the synthesis of several metal complexes of prodigiosenes, so as to be able to evaluate the antimalarial activity of this new structural class. Prodigiosenes can be considered as a dipyrrin extended with a pyrrolyl substituent, and are thus good candidates for metal complexation.[22] Indeed both nitrogen atoms of the dipyrrin moiety could be involved in chelation to the metal centre. Alternatively the three nitrogen atoms of the entire dipyrrinato-pyrrolyl skeleton could all be coordinated. Homoleptic dimeric zinc complexes of prodigiosenes[11d,23] and the natural compound **1**[24] are known, as is an oxidised Cu(II):prodigiosin complex[24] proposed to be partially responsible for the anticancer properties of prodigiosin.[25] Several homoleptic zinc complexes, MP_2, of our prodigiosenes (P) were thus prepared (Scheme 6).[26]

C-ring benzyl ester prodigiosenes with non-modified (**16**) and modified A-rings (**24**, **25**, **28**, **33**) were obtained as their zinc-complexes (**34–38**) in moderate-to-good yields. Complex **39** with an alkyl chain in the C-ring β-position, was obtained quantitatively using the same conditions. As expected, and in keeping with previous work involving dipyrrins and prodigiosenes,[24,27] all zinc complexes were obtained as single discrete ZnP_2 complexes, with no mass spectral evidence to the contrary.



Scheme 6 Synthesis of zinc complexes of prodigiosenes and dipyrrins.



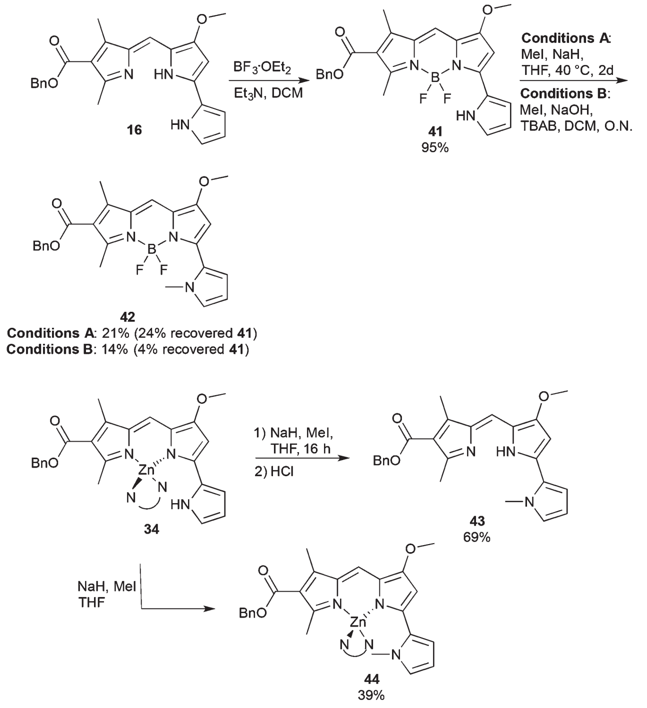
Scheme 7 Metal complexes of prodigiosenes; n.r. = no reaction.

Dipyrrins form complexes with numerous M(II)[27,28] and M(III) metals.[28c,29] We consequently attempted the synthesis of transition metal complexes of prodigiosenes (Scheme 7). Using the same protocol as for the formation of prodigiosene Zn complexes but using $Co(OAc)_2$,[26] a complex of cobalt(II) (MP_2, **40**) was obtained in 30% yield using benzyl ester prodigiosene **16** as starting material. Surprisingly, although dipyrrins are known to form metal(III) complexes, the formation of prodigiosene complexes of Co(III),[29b] Fe(III)[29b] and In(III)[29f] failed in our hands, perhaps due to steric hindrance at the C-ring α-position (Scheme 7).[30]

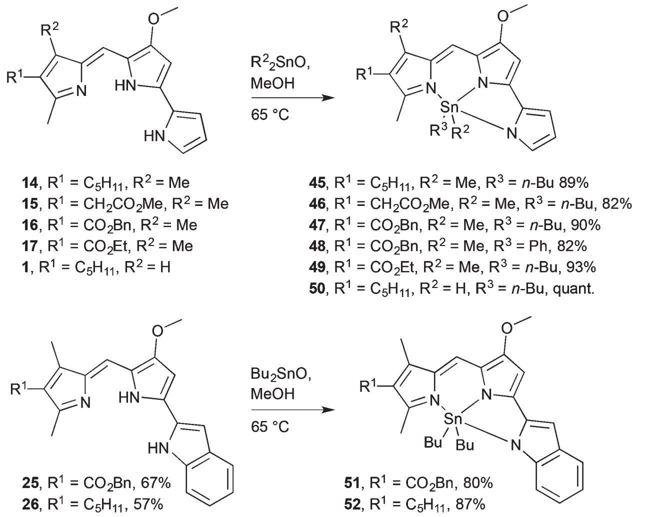
To investigate the influence of the nitrogen atom of the prodigiosene A-ring upon consequent antimalarial activity, we protected the A-ring pyrrolic moiety with a methyl group. As the fully delocalised system of the prodigiosene prevents selective protection of the A-ring pyrrole, we took advantage of the fact that prodigiosenes easily form metal complexes to sequester the B- and C-rings: the protected prodigiosene could then be methylated at the A-ring. As such, the dipyrrinato unit of prodigiosene **16** was protected (Scheme 8).[31,32]

F-BODIPY **41** was then subjected to classic methylation conditions using NaH and methyl iodide (Conditions A). Unfortunately only 21% of the protected prodigiosene **42** was isolated after 2 days of reaction along with 24% of starting material (**41**). Changing the conditions to involve NaOH, TBAB and methyl iodide in DCM[33] was equally unsuccessful and gave only 14% of the expected compound **42** (Conditions B). Fortunately, the use of zinc(II) proved to be a successful strategy for protecting the prodigiosene for this purpose: methylation of the zinc complex **34** (Scheme 8) occurred smoothly in the presence of NaH and methyl iodide to give prodigiosene **43** in 69% yield after a quench using aqueous HCl, followed by purification. Without quenching with HCl, the prodigiosene could be isolated as the zinc metal complex **44** (Scheme 8).

We have previously reported that prodigiosene tin complexes **47** and **48** (Scheme 9) exhibit a low acute systemic



Scheme 8 Methyl protection of the A-ring pyrrole of prodigiosene.



Scheme 9 Preparation of tin complexes of prodigiosenes.

toxicity compared to the natural product free-base prodigiosin **1**.[9g] The suggestion that tin complexes of prodigiosenes could be better tolerated than prodigiosin itself lead us to evaluate the antimalarial activity of several prodigiosene tin complexes. Prodigiosenes substituted at the C-ring with alkyl (Scheme 9, **14**, **15**) and carboxyl groups (**16**, **17**), as well as A-ring modified prodigiosenes (**25**, **26**) and the natural product itself (**1**), were thus subjected to tin complexation using Bu_2SnO and Ph_2SnO.[34] Stable tin complexes **45–52** were obtained in excellent yield after purification over alumina. Akin to the zinc complexes, tin complexes of prodigiosenes were obtained as discrete MP entities as demonstrated using LRMS spectrometry. These tin complexes exhibited considerable fluorescence, in keeping with previously reported compounds.[34]

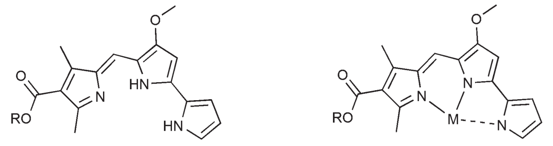
Biological activity

All synthesised prodigiosenes, as well as the natural product **1**,[35] were evaluated against the human 3D7 strain of *Plasmodium falciparum*. Antimalarial activity was determined as the half maximal inhibitory concentration (IC_{50}). So as to facilitate discussion of valuable activity levels, efficient antimalarial activity can be appreciated as excellent ($IC_{50} < 1$ μM) and good (1 μM < IC_{50} < 20 μM),[36] following previously published criteria.

The antimalarial activity of C-ring ester prodigiosenes was first evaluated (Table 1). Benzyl, ethyl and isopropyl esters **16–18** exhibited promising IC_{50} values around 1 μM, but fell significantly short of the activity of the natural product prodigiosin **1** (11 nM) or chloroquine (15 nM). In agreement with previously reported data that showed that substitution with either a very short or an excessively long alkyl chain dramatically decreases antimalarial activity of prodigiosenes,[14] the long chain ester **19** was not effective against 3D7. Interestingly dibutyl tin complexes of A-ring ester-bearing prodigiosenes **47** and **49** exhibited improved IC_{50} values (116 nM and 521 nM, respectively) compared to their corresponding free-base prodigiosenes **16** and **17** (IC_{50} = 0.9 μM and 1.5 μM, respectively) but the cobalt-prodigiosene dimer (CoP_2, where P = prodigiosene, **40**), the diphenyl tin complex (**48**), the zinc dimer (ZnP_2, **34**) and BF_2 (**41**) complexes were not as effective as their free-base ligand (**16**).

We then turned our attention to the influence of the nature of the A-ring upon the antimalarial activity of prodigiosenes. Indeed, a previous study affirmed the importance of the A-ring

Table 1 *In vitro* antimalarial activity of C-ring ester prodigiosenes



R	IC_{50} (free-base)	M	IC_{50} (complex)
Chloroquine	15 nM		
Prodigiosin	11 nM (**1**)		
-Benzyl	0.9 μM (**16**)	$SnBu_2$	116 nM (**47**)
-Benzyl		Co[a]	5 < IC_{50} < 50 μM (**40**)
-Benzyl		$SnPh_2$	5 < IC_{50} < 50 μM (**48**)
-Benzyl		Zn[a]	≈50 μM (**34**)
-Benzyl		BF_2 [b]	No effect (**41**)
-Ethyl	1.5 μM (**17**)	$SnBu_2$	521 nM (**49**)
-ipropyl	1.0 μM (**18**)		
$-C_{14}H_{28}$	No effect (**19**)		

[a] The Co and Zn complexes are dimeric, *i.e.* MP_2 where P = prodigiosene with chelating dipyrrinato units and uncomplexed N–*H* moieties on the A-ring pyrroles. [b] For the BF_2 complex the dipyrrinato unit complexes with boron leaving an uncomplexed N–*H* on the A-ring pyrrole.

pyrrole for parasiticidal activity while substituents at α- and β′-positions of the C-ring can be varied.[14] For this purpose we compared the IC_{50} values of several benzyl ester prodigiosenes substituted with various R^2 groups (Table 2). Protection of the pyrrole A-ring with a methyl group (**43**) considerably decreased the antimalarial activity of the benzyl ester prodigiosene **16** (compare IC_{50} of 938 nM for **16** *vs.* 5 > IC_{50} > 50 μM for **43**) showing that the presence of the N–*H* moiety of the A-ring is essential. This is supported by the moderate IC_{50} values of prodigiosenes substituted with a phenyl (**24**) or ethyl group (**28**). Replacement of the A-ring pyrrole with an indole slightly decreases the antimalarial activity (compare IC_{50} = 0.9 μM for **16** and IC_{50} = 5.6 μM for **25**) but as shown in Table 1, yet again the activity can be increased by complexation of the prodigiosene with dibutyl tin (**51**, IC_{50} 4.7 μM, compared to 5.6 μM for **25**). As previously, zinc complexes have almost no effect on plasmodium 3D7 (**44**, **35**, **37**, **36**, **38**). Interestingly, although omission of the methoxy group at the B-ring of prodigiosenes induces a decreased cytotoxic activity against cancer cells,[37] substitution with a methyl group does not seem to be detrimental to antimalarial activity (compare **33** and **28**).

The antimalarial activity of C-ring alkyl prodigiosenes was also explored (Table 3). Prodigiosene **14** is a close analogue of the natural prodigiosin (**1**), substituted with only one extra methyl group at the β′-position of the C-ring (Fig. 1). We previously showed that the presence of the extra methyl group allows a shorter and easier synthesis compared to prodigiosin itself,[37] and that analogue **14** possesses similar properties to the natural compound (*i.e.*, anticancer, transmembrane anion transport and DNA cleavage activity).[17b] Here, compound **14** exhibits an excellent IC_{50} value in the same range as prodigiosin **1** (Table 3), demonstrating that the extra methyl group is not detrimental for antimalarial activity, further complementing its role as a model for the natural product prodigiosin.

As shown in Table 3, substitution of the A-ring pyrrole of prodigiosene **14** with an indolic group decreases the activity slightly, yet both are in the excellent range (Table 3, compare IC_{50} = 19 nM for **14** and IC_{50} 98 nM for **26**). For prodigiosin **1**

Table 2 *In vitro* antimalarial activity of dipyrrins and prodigiosenes with a modified A-ring

R^1	R^2	IC_{50} (free-base)	M	IC_{50} (complex)
Prodigiosin		11 nM (**1**)		
-OMe	-2-Pyrrolyl	0.9 μM (**16**)		
-OMe	-1-Me-2-pyrrolyl	5 < IC_{50} < 50 μM (**43**)	Zn^a	≈50 μM (**44**)
-OMe	-Phenyl	5 < IC_{50} < 50 μM (**24**)	Zn^a	No effect (**35**)
-OMe	-Ethyl	5 < IC_{50} < 50 μM (**28**)	Zn^a	No effect (**37**)
-OMe	-2-Indolyl	5.6 μM (**25**)	$SnBu_2$	4.7 μM (**51**)
-OMe	-2-Indolyl		Zn^a	≈50 μM (**36**)
-Me	-Me	4.7 μM (**33**)	Zn^a	No effect (**38**)

[a] The Zn complexes are dimeric, *i.e.* MP_2 where P = prodigiosene with chelating dipyrrinato units and uncomplexed N–*H* moieties on the A-ring pyrroles.

Table 3 *In vitro* antimalarial activity of C-ring alkyl and carbonyl prodigiosenes

R^1	R^2	IC_{50} (free-base)	M	IC_{50} (complex)
Prodigiosin		11 nM (**1**)	$SnBu_2$	7.1 nM (**50**)
$-C_5H_{11}$	2-Pyrrolyl	19 nM (**14**)	$SnBu_2$	18 nM (**45**)
$-C_5H_{11}$	2-Indolyl	98 nM (**26**)	$SnBu_2$	1.4 μM (**52**)
$-C_5H_{11}$	2-Indolyl		Zn^a	5 < IC_{50} < 50 μM (**39**)
$-CH_2CO_2Me$	2-Pyrrolyl	1.5 μM (**15**)	$SnBu_2$	56 nM (**46**)
$-(CO)C_4H_8CO_2Me$	2-Pyrrolyl	5 < IC_{50} < 50 (**20**)		
$-(CO)C_2H_4CO_2Et$	2-Pyrrolyl	5 < IC_{50} < 50 (**21**)		
$-(CO)C_4H_8CO_2H$	2-Pyrrolyl	≈50 μM (**22**)		

[a] The Zn complex is dimeric, *i.e.* MP_2 where P = prodigiosene with a chelating dipyrrinato unit and an uncomplexed N–*H* moiety on the A-ring pyrrole.

and compounds **14** and **26**, complexation with dibutyl tin did not improve their antimalarial activity. However tin complexation was beneficial for prodigiosene **15**, bearing an ethanoate side-chain. Indeed the free-base prodigiosene **15** exhibited an IC_{50} of 1.5 μM and its dibutyl tin complex (**46**) an IC_{50} of 56 nM. Once again zinc complexation decreased the antimalarial activity (zinc complex **39** exhibited an $IC_{50} > 5$ μM). Compounds **20–22** show good anticancer properties,[11d] but are poorly cytotoxic against the plasmodium 3D7, indicating a clear decoupling of activity.

These results can be assembled to probe a brief structure activity relationship. Although it would be premature to debate modes of action for prodigiosenes and their complexes against malaria parasites, from these experiments it appears that prodigiosenes substituted at the β′-position of the C-ring with an alkyl chain better inhibit the malaria parasite 3D7 than prodigiosenes substituted with an ester group. This suggests that decreasing the acidity of the prodigiosene, induced by the presence of the ester group, is detrimental to the inhibition activity (prodigiosin $pK_a = 8.2$, pK_a C-ring ester prodigiosene = 6.5).[17b] The natural product prodigiosin is known to interact with DNA by intercalation with a preference for the AT sequences.[38] From our studies of prodigiosene–DNA interaction (CT-DNA melting studies and UV/vis titrations of CT-DNA), we found that ethyl ester prodigiosene **17** (which demonstrates good antimalarial activity) and prodigiosenes **20** and **22** (which demonstrate poor antimalarial activity) exhibit similar DNA-binding profiles, presumably *via* an intercalative mode (see ESI†). As such, the antimalarial activity of **17** could be related to its ability to intercalate DNA strongly. However, **20** and **22** also interact with DNA strongly, yet their lack of antimalarial activity points toward either a target other than DNA; differential uptake/efflux/metabolism; or an alternative parasite–drug interaction.

The SAR study also suggests that the presence of the nitrogen atom at the A-ring is necessary for a good anti-plasmodial activity *in vitro*. Contrary to what was observed for the anticancer properties of prodigiosenes,[37] it appears that the presence of the B-ring methoxy group is not essential for antimalarial activity against 3D7. We also observed that dibutyl tin complexation of prodigiosenes could in some cases increase the inhibition property of the free-base prodigiosene. The increased activity in that case could, in part, be explained by increased lipophilicity affecting uptake.

Conclusions

Although the antimalarial properties of natural prodigiosins have long been reported,[12a] the antimalarial activity of prodigiosene analogues has been poorly studied. Recently, the cytotoxic activity of prodigiosene analogues substituted at the α-and β′-position of the C-ring against D6 and Dd2 falciparum strains was reported and showed promising results.[14] Here we report the antimalarial activity of analogues of the natural prodigiosin **1** bearing an extra methyl group at the β′-position, alongside a variety of other substituents, against the 3D7 *Plasmodium falciparum* strain. We demonstrate that the extra methyl group allows a short and facile synthesis of prodigiosene analogues, and that this addition is not detrimental to antimalarial activity. Indeed, the close analogue **14** exhibiting only the extra methyl group compared to the natural product **1** seems as effective as prodigiosin **1** itself against 3D7 and is deemed to exhibit excellent[36] activity against 3D7. This compound previously showed similar anticancer properties to prodigiosin **1**[17b] and we anticipate that this easily accessible material will be used as a model for the natural compound (**1**).

This study also demonstrated the importance of the presence of the nitrogen atom in the A-ring for antimalarial activity. Prodigiosenes with alkyl substituents at the C-ring β-position were more cytotoxic against 3D7 than prodigiosenes with carbonyl substituents. Zn, Co, BF_2 and diphenyl tin complexes of prodigiosenes were, at best, poorly effective against the human malaria parasite *in vitro*. However, dibutyl tin complexes of prodigiosenes were as effective or more effective than their free-base counterparts, perhaps due to the lipophilicity of the dibutyl tin moiety. Many of the prodigiosenes reported herein exhibit activity against 3D7 that has been classified as "good", with several in the "excellent" class:[36] analogue **14** shows particular promise, with activity at nanomolar concentrations, as do the tin complexes **45** and **47**. Cognisant of the low toxicity profile of prodigiosene tin complexes,[9g] these results could open the door to new antimalarial agents.

Experimental

General information

All chemicals were purchased and used as received unless otherwise indicated. Moisture-sensitive reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon. Solutions of air- and moisture-sensitive compounds were introduced *via* syringe or cannula through a septum. Flash chromatography was performed using Silicycle ultra pure silica (230–400 mm) or 150 mesh Brockmann III activated neutral or basic alumina oxide as indicated. The NMR spectra were recorded using a 500 MHz or 300 MHz spectrometer instrument using $CDCl_3$ as solvent and are reported in part per million (δ) using the solvent signals at 7.26 ppm for ^1H and at 77.16 ppm for ^{13}C as an internal reference with *J* values given in hertz. Mass spectra were obtained using TOF and LCQ Duo ion trap instruments operating in ESI+ mode. Melting points were determined using a Fisher-Johns melting point apparatus, and are uncorrected. Compounds **1**,[35] **5**,[17b] **6**,[17c] **7** and **8**,[17a] **9** and **10**,[17b] **11** and **12**,[11d] **13**,[39] **14**,[17b] **15**,[17c] **16** and **17**,[17a] **18** and **19**,[17b] **20**,[11d] **21** and **22**,[39] **30** and **31**[17a] **32**,[21] **34**,[17b] **47–49**[34] were prepared according to literature procedures.

(*Z*)-Benzyl 2-((3-methoxy-5-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate 23. To a suspension of (*Z*)-benzyl 5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate[17a] (2.0 g 5.67 mmol), in dry DCM (300 mL) at 0 °C was slowly added Tf_2O (2.7 mL, 15.9 mmol). After 4 h stirring at this temperature, the reaction was quenched with sat. aqueous $NaHCO_3$ (400 mL), then extracted with DCM (3 × 200 mL). The combined organic layers were washed with brine, and then dried (Na_2SO_4). After evaporation of the solvents under reduced pressure, the crude material was purified using flash column chromatography (SiO_2, EtOAc–hexane 2/8) to give a yellow solid (1.5 g, 55%). ^{1}H NMR ($CDCl_3$, 300 MHz) 2.42 (s, 3H), 2.57 (s, 3H), 3.90 (s, 3H), 5.30 (s, 2H), 5.43 (s, 1H), 7.12 (s, 1H), 7.30–7.44 (m, 5H), 11.01 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 11.7, 15.2, 59.0, 65.7, 87.6, 113.9, 118.7 (q, *J* = 319 Hz), 119.0, 126.1, 128.2, 128.2, 128.7, 133.5, 135.4, 136.6, 145.0, 161.9, 164.9, 168.2. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{20}F_3N_2O_6S_1$, 485.0989; found, 485.0996.

General procedure 1 for the synthesis of prodigiosenes 24–27

Compound **5** or **23** (0.48 mmol, 1 eq.) was dissolved in DME (9 mL) then LiCl (60 mg, 1.44 mmol, 3 eq.) and boronic acid (121 mg, 0.57 mmol, 1.2 eq.) were added. The solution was degassed by bubbling with N_2, and then palladium tetrakis-(PPh_3) (56 mg, 10 mol%) was added. Then a degassed 2 M solution of Na_2CO_3 was added (1.0 mL, 1.92 mmol, 4 eq.) and the suspension was stirred at 85 °C for 18 h. After cooling the solution was poured into water (100 mL) and extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (100 mL), and then dried (Na_2SO_4).

(*Z*)-Benzyl 2-((3-methoxy-5-phenyl-1*H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate 24. Obtained following general procedure 1 and then purification using chromatography (Al_2O_3 basic type III, EtOAc–hexane 1/9) as an orange solid (23%, 62 mg). Mp 169 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 2.44 (s, 3H), 2.64 (s, 3H), 3.93 (s, 3H), 5.32 (s, 2H), 6.09 (s, 1H), 6.98 (s, 1H), 7.33–7.35 (m, 1H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.43–7.48 (m, 5H), 7.98 (d, *J* = 7.2 Hz, 2H), 11.00 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 11.8, 15.5, 58.5, 65.5, 95.1, 113.3, 115.1, 127.0, 127.6, 128.0, 128.2, 128.6, 128.7, 130.1, 132.6, 134.8, 136.8, 141.9, 143.5, 165.4, 166.6, 168.5. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_3$, 413.1860; found, 413.1864.

(*Z*)-Benzyl 2-(2-((5-(1*H*-indol-2-yl)-3-methoxy-1*H*-pyrrol-2-yl)-methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-2-oxoacetate 25. Obtained following the general procedure 1. Then the crude material was dissolved in a mixture of methanol–chloroform–water 3/3/1.5 mL and K_2CO_3 (3 eq.) was added. The reaction mixture was stirred for 2 days at reflux temperature then water (50 mL) was added and the mixture was extracted with DCM (3 × 40 mL). The combined organic layers were washed with brine then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude product was purified using column chromatography (Al_2O_3 type III basic, EtOAc–hexanes 2/8) to give a red solid (67%, 203 mg). Mp 113 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 2.25 (br s, 3H), 2.40 (s, 3H), 4.05 (s, 3H), 5.23 (s, 2H), 6.26 (s, 1H), 6.98–7.03 (m, 3H), 7.11–7.15 (m, 2H), 7.31–7.36 (m, 5H), 7.54 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 11.9, 13.3, 58.9, 65.5, 96.7, 106.7, 111.6, 113.9, 114.9, 120.2, 121.4, 124.3, 126.2, 128.0, 128.2, 128.6, 133.3, 134.2, 136.7, 138.0, 139.4, 145.0, 161.0, 165.0, 169.4 (1 carbon non accounted for). HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{28}H_{26}N_3O_3$, 452.1969; found, 451.1967.

(*Z*)-2-(5-((3,5-Dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-4-methoxy-1*H*-pyrrol-2-yl)-1*H*-indole 26. Obtained following the general procedure 1. Then the crude material was dissolved in a mixture of methanol–chloroform–water 3/3/1.5 mL and K_2CO_3 (3 eq.) was added. The reaction mixture was stirred overnight at reflux temperature then water (50 mL) was added and the product was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with brine then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude was purified using column chromatography (Al_2O_3 type III basic, EtOAc–hexanes 1/9) to give a red glass (57%, 94 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.83 (t, *J* = 7.2 Hz, 3H), 1.20–1.30 (m, 6H), 1.72 (s, 3H), 2.10 (s, 3H), 2.16 (t, *J* = 7.2 Hz, 2H), 4.07 (s, 3H), 6.34 (s, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.87 (s, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 7.10 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 10.5, 14.2, 22.6, 24.2, 30.4, 32.0, 58.7, 95.9, 104.3, 111.7, 115.8, 119.6, 120.8, 123.2, 124.2, 126.1, 128.6, 132.2, 134.3, 136.0, 137.8, 139.5, 157.7, 168.7. UV (DCM) λ_{max} (ε): 578 nm (118 000 L mol^{-1} cm^{-1}). HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{25}H_{30}N_3O_1$, 388.2383; found, 388.2377.

(*Z*)-Benzyl 2-((5-ethyl-3-methoxy-1*H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate hydrochloride 28. Under nitrogen to a Schlenk tube containing (*Z*)-benzyl 2-((5-bromo-3-methoxy-1*H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate **7** (200 mg, 0.48 mmol) and Pd(dppf)Cl_2 (10.4 mg, 0.014 mmol) was added dioxane (4 mL). The resulting solution was degassed with nitrogen (3 times vacuum/nitrogen refill cycle) then Et_2Zn (960 μL, 0.96 mmol) was added. The reaction vessel was heated at 100 °C for 1 hour, then cooled to room temperature. The reaction was quenched by the addition of a few drops of methanol, then HCl 1 M (20 mL) was added and the reaction mixture was extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (30 mL), then dried (Na_2SO_4). After evaporation of the solvents under vacuum the resulting solid was triturated with MeOH, filtered (Millipore) and washed 3 times with MeOH to give an orange solid (103 mg, 53%). Mp 192 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 1.36 (t, *J* = 7.5 Hz, 3H), 2.53 (s, 3H), 2.83 (s, 3H), 3.05 (q, *J* = 7.5 Hz, 2H), 4.00 (s, 3H), 5.30 (s, 2H), 5.77 (s, 1H), 7.30 (s, 1H), 7.33–7.42 (m, 5H), 13.60 (br s, 1H), 13.95 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.2, 12.5, 15.2, 23.1, 59.2, 66.1, 95.1, 116.7, 118.2, 120.7, 124.1, 128.3, 128.7, 136.2, 144.9, 154.0, 164.2, 167.4, 168.1 (1 carbon non accounted for). HRMS-ESI (*m*/*z*): $[M - Cl]^+$ calcd for $C_{22}H_{25}N_2O_3$, 365.1860; found, 365.1868.

(*Z*)-Benzyl 2-((3,5-dimethyl-1*H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate hydrobromide 33. To a mixture of THF–MeOH (1.6/1.6 mL) was added benzyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate **31** (372 mg, 1.62 mmol) and 3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (**32**) (100 mg, 0.81 mmol). To the resulting solution was added HBr (48%, 156 μL, 1.78 mmol) and a precipitate formed instantly. The reaction mixture was cooled to 0 °C for an hour, and then filtered (Millipore). The crude solid was washed with Et_2O (3 × 15 mL) to give the product as a yellow solid (300 mg, quant.) Mp 226 °C. ^1H NMR ($CDCl_3$, 500 MHz) 2.40 (s, 3H), 2.59 (s. 3H), 2.71 (s, 3H), 2.91 (s, 3H), 5.32 (s, 2H), 6.23 (s, 1H), 7.24 (s, 1H), 7.34–7.42 (m, 5H), 13.24 (br s, 1H), 13.58 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.4, 12.5, 15.0, 15.4, 66.4, 117.8, 119.4, 121.3, 125.0, 128.4, 128.5, 128.7, 128.8, 135.9, 147.3, 149.2, 156.4, 160.5, 163.5. HRMS-ESI (*m/z*): $[M - Br]^+$ calcd for $C_{21}H_{23}N_2O_2$, 335.1754; found, 335.1746.

General procedure 2 for the synthesis of Zn complexes

To a solution of prodigiosene (1 eq.) in $CHCl_3$ (0.04 M) was added a solution of $Zn(OAc)_2{\cdot}2H_2O$ (2.4 eq.) and $NaOAc{\cdot}3H_2O$ (2.4 eq.) in MeOH (0.2 M). After 5 h stirring at room temperature, water (20 mL) was added and the solution was extracted with DCM (3 × 20 mL). the combined organic layers were washed with water (40 mL) and brine (40 mL), and then dried (Na_2SO_4).

Prodigiosene zinc(II) complex 35. Obtained following general procedure 2 then, after concentration, the residue was purified using flash chromatography (Al_2O_3 III basic, EtOAc–hexane 1/9 then 2/8) to give a red solid (48 mg, 90%). Mp 181 °C. ^1H NMR ($CDCl_3$, 500 MHz) 2.12 (s, 6H), 2.53 (s, 6H), 3.91 (s, 6H), 5.21–5.24 (ABq, *J* = 12.5 Hz, 4H), 5.84 (s, 2H), 7.01 (t, *J* = 7.7 Hz, 4H), 7.11 (t, *J* = 7.5 Hz, 2H), 7.27–7.30 (m, 6H), 7.33–7.35 (m, 6H), 7.38–7.39 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.4, 17.3, 58.3, 65.4, 95.7, 116.8, 121.6, 126.9, 127.9, 128.1, 128.2, 128.6, 128.8, 131.4, 134.3, 134.4, 137.0, 143.6, 157.9, 161.9, 165.6, 166.7. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{52}H_{46}N_4O_6Zn_1$, 886.2703; found, 886.2674.

Prodigiosene zinc(II) complex 36. Obtained following general procedure 2 then, after concentration, the residue was purified using flash chromatography (Al_2O_3 III neutral, EtOAc–hexane 3/7) to give a red solid (36 mg, 68%). Mp 266 °C. ^1H NMR ($CDCl_3$, 500 MHz) 2.22 (s, 6H), 2.62 (s, 6H), 4.00 (s, 6H), 5.21 (s, 4H), 6.21 (s, 2H), 6.82–6.85 (m, 4H), 7.01 (t, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 2H), 7.27–7.38 (m, 10H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.53 (s, 2H), 8.91 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.4, 17.5, 58.6, 65.6, 97.1, 107.2, 111.6, 117.7, 119.7, 120.6, 121.1, 124.3, 128.0, 128.2, 128.3, 128.6, 131.7, 133.9, 136.7, 137.8, 143.6, 154.5, 158.1, 165.2, 166.8 (1 carbon non accounted for). HRMS-APCI (*m/z*): $[M + H]^+$ calcd for $C_{56}H_{49}N_6O_6Zn$, 965.3000; found, 965.2970.

Zinc(II) complex 37. Obtained following general procedure 2 then, after concentration, the residue was triturated with MeOH, filtered (Millipore) and washed with MeOH (3 × 5 mL) to give a yellow solid (63 mg, 61%). Mp/dec > 220 °C. ^1H NMR ($CDCl_3$, 500 MHz) 0.88 (t, *J* = 7.7 Hz, 6H), 2.19 (s, 6H), 2.22 (q, *J* = 7.7 Hz, 4H), 2.52 (s, 6H), 3.89 (s, 6H), 5.24 (s, 4H), 5.59 (s, 2H), 7.25 (s, 2H), 7.27–7.30 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 4H), 7.40 (d, *J* = 7.5 Hz, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.3, 12.8, 17.6, 25.6, 58.3, 65.3, 95.2, 115.9, 120.7, 127.9, 128.2, 128.6, 130.1, 133.5, 137.1, 142.2, 156.8, 165.8, 167.3, 169.2. HRMS-APCI (*m/z*): $[M + H]^+$ calcd for $C_{44}H_{47}N_4O_6Zn$, 791.2782; found, 791.2745.

Zinc(II) complex 38. Obtained following general procedure 2 then, after concentration, the residue was triturated with MeOH, filtered (Millipore) and washed 3 times with MeOH to give a yellow solid (30 mg, 68%). ^1H NMR ($CDCl_3$, 500 MHz) 1.93 (s, 6H), 2.19 (s, 6H), 2.33 (s, 6H), 2.55 (s, 6H), 5.25 (s, 4H), 6.08 (s, 2H), 7.16 (s, 2H), 7.27–7.300 (m, 2H), 7.34 (t, *J* = 7.2 Hz, 4H), 7.40 (d, *J* = 7.2 Hz, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.0, 12.4, 16.8, 17.7, 65.4, 116.6, 119.7, 123.1, 128.0, 128.3, 128.6, 134.4, 137.0, 139.2, 143.8, 146.0, 158.0, 163.1, 165.6. HRMS-APCI (*m/z*): $[M + H]^+$ calcd for $C_{42}H_{43}N_4O_4Zn$, 731.2570; found, 731.2577.

Zinc(II) complex 39. Obtained following general procedure 2 then, after concentration, the residue was purified using column chromatography (Al_2O_3 type III basic, DCM–hexanes 3/7) to give a red film (55 mg, quant.). ^1H NMR ($CDCl_3$, 500 MHz) 0.79 (t, *J* = 7.5 Hz, 6H), 1.15–1.25 (m, 8H), 1.30 (quint., *J* = 7.5 Hz, 4H), 1.94 (s, 6H), 2.25–2.30 (m, 10H), 3.98 (s, 6H), 6.26 (s, 2H), 6.71 (d, *J* = 1.5 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 6.97 (t, *J* = 7.0 Hz, 2H), 7.07 (t, *J* = 7.0 Hz, 2H), 7.35 (s, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 9.09 (br s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) 10.2, 14.1, 14.9, 22.6, 24.8, 30.1, 31.7, 58.2, 96.2, 103.6, 111.6, 118.4, 119.9, 120.3, 122.7, 128.0, 128.4, 130.2, 133.3, 135.7, 137.3, 138.5, 148.5, 158.2, 163.9. LRMS 837.3 $[M + H]^+$. HRMS-APCI (*m/z*): $[M + H]^+$ calcd for $C_{50}H_{57}N_6O_2Zn$, 837.3829; found, 837.3818.

Prodigiosene cobalt(II) complex 40. To a solution of prodigiosene **16** (50 mg, 0.12 mmol) in $CHCl_3$ (12 mL) was added a solution of $Co(OAc)_2{\cdot}4H_2O$ (77 mg, 0.31 mmol) and $NaOAc{\cdot}3H_2O$ (42 mg, 0.31 mmol) in MeOH (4 mL). After 30 min stirring at room temperature, water (20 mL) was added and the solution was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine, and then dried (Na_2SO_4). After concentration under vacuum the residue was purified using flash chromatography (Al_2O_3 III neutral, EtOAc–hexane 5/5) to give a red solid (31 mg, 30%). Mp = 262 °C. As this complex is paramagnetic no NMR spectra could be obtained. HRMS-APCI (*m/z*): $[M + H]^+$ calcd for $C_{48}H_{45}CoN_6O_6$, 860.2727; found, 860.2697.

2-((Benzyloxy)carbonyl)-5,5-difluoro-9-methoxy-1,3-dimethyl-7-(1*H*-pyrrol-2-yl)-5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborinin-4-ium-5-uide 41. The HCl salt of prodigiosene 16 (300 mg, 0.68 mmol) was dissolved in anhydrous DCM (40 mL) under nitrogen. Triethylamine (570 μL, 4.08 mmol) was added and the reaction was stirred for 5 min before $BF_3{\cdot}OEt_2$ (970 μL, 6.8 mmol) was added. The reaction mixture was stirred for 16 h at room temperature, and then quenched *via* the addition of 1 M HCl (50 mL). The crude mixture was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (50 mL), and dried (Na_2SO_4). After evaporation of the solvent the crude material was purified using flash column chromatography (Al_2O_3 neutral type III, DCM–hexanes, 5/5, 6/4 then 7/3) to give a dark purple film (95%, 292 mg). Mp 280 °C. ^1H NMR ($CDCl_3$, 500 MHz) 2.42 (s, 3H), 2.80 (s, 3H), 3.99 (s, 3H), 5.32 (s, 2H), 6.14 (s, 1H), 6.37–6.39 (m, 1H), 6.97–6.99 (m, 1H), 7.16 (s, 1H), 7.18–7.19 (m, 1H), 7.31–7.34 (m, 1H), 7.37–7.40 (m, 2H), 7.43–7.44 (m, 2H) 10.49 (br s, 1H). ^{13}C NMR

($CDCl_3$, 125 MHz) 12.0, 14.5, 58.7, 65.7, 97.3, 111.7, 114.9, 117.3, 118.8, 123.5, 126.5, 128.1, 128.2, 128.7, 129.4, 129.5, 136.4, 136.7, 151.5, 153.0, 164.4, 165.1. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{24}H_{22}BF_2N_3O_3$, 449.1717; found, 449.1705.

2-((Benzyloxy)carbonyl)-5,5-difluoro-9-methoxy-1,3-dimethyl-7-(1-methyl-1*H*-pyrrol-2-yl)-5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*][1,3,2]diazaborinin-4-ium-5-uide 42. Method A: to a suspension of NaH (60% in grease, 5.5 mg, 0.13 mmol) in anhydrous THF (3 mL) under nitrogen was added prodigiosene **41** (50 mg, 0.11 mmol) at 0 °C. After 30 min stirring at room temperature MeI (20 μL, 0.33 mmol) was added and the reaction was heated at 40 °C for two days. After cooling to room temperature a saturated solution of ammonium chloride (20 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (50 mL) then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude product was purified using column chromatography (Al_2O_3 type III basic, EtOAc–hexanes 3/7) to give a dark pink solid (21%, 11 mg).

Method B: to a solution of prodigiosene **41** (75 mg, 0.17 mmol) in DCM (1.5 mL) was added MeI (11.4 μL, 0.18 mmol), followed by TBAB (5.5 mg, 0.017 mmol) and an aqueous solution of NaOH 12 M (80 μL, 12 eq.). The reaction mixture was heated at 40 °C for 24 hours then cooled to room temperature and quenched with HCl (1 M, 20 mL). The reaction mixture was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using column chromatography (Al_2O_3 type III basic, EtOAc–hexanes 3/7) to give a dark pink solid (14%, 11 mg). Mp 203 °C. ^1H NMR ($CDCl_3$, 500 MHz) 2.44 (s, 3H), 2.77 (s. 3H), 3.77 (s, 3H), 3.97 (s, 3H), 5.30 (s, 2H), 5.88 (s, 1H), 6.29–6.31 (m, 1H), 6.86 (s, 1H), 7.28–7.34 (m, 3H), 7.36–7.39 (m, 2H), 7.42–7.43 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.1, 14.8, 36.5, 58.7, 65.8, 98.8, 110.0, 117.8, 118.0, 118.1, 118.1, 125.4, 128.1, 128.2, 128.7, 129.1, 130.4, 136.6, 139.6, 151.4, 155.8, 164.2, 164.9. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{24}B_1F_2N_3Na_1O_1$, 486.1771; found, 486.1758.

(*Z*)-Benzyl 2-((4-methoxy-1′-methyl-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)-methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate 43. To a suspension of NaH (60% in grease, 6 mg, 0.15 mmol) in anhydrous THF (3 mL) under nitrogen was added prodigiosene **34** (50 mg, 0.06 mmol) at 0 °C. After 30 min stirring at room temperature, MeI (11 μL, 0.17 mmol) was added and the reaction was stirred during 24 hours. Then, an HCl solution (1 M, 20 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (50 mL) then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using column chromatography (Al_2O_3 type III basic, EtOAc–hexanes 2/8) to give an orange solid (69%, 33 mg). ^1H NMR ($CDCl_3$, 500 MHz) 2.41 (s, 3H), 2.53 (s. 3H), 3.89 (s, 3H), 4.13 (s, 3H), 5.31 (s, 2H), 5.92 (s, 1H), 6.21–6.22 (m, 1H), 6.71–6.72 (m, 1H), 6.80–6.81 (m, 2H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 11.6, 15.1, 37.8, 58.5, 65.4, 97.0, 108.8, 111.7, 112.8, 115.5, 127.5, 128.0, 128.2, 128.6, 128.8, 129.8, 136.9, 141.3, 142.9, 160.0, 165.6, 167.3 (1 carbon non accounted for). HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{25}H_{26}N_3O_3$, 416.1969; found, 416.1984.

Prodigiosene zinc(II) complex 44. To a suspension of NaH (60% in grease, 9 mg, 0.23 mmol) in anhydrous THF (4 mL) under nitrogen was added prodigiosene **34** (50 mg, 0.06 mmol) at 0 °C. After 30 min stirring at room temperature, MeI (14 μL, 0.23 mmol) was added and the reaction was stirred for 24 hours. Then, water (20 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (50 mL), and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using column chromatography (Al_2O_3 type III basic, EtOAc–hexanes 4/6) to give a dark red film (39%, 29 mg). ^1H NMR ($CDCl_3$, 500 MHz) 2.10 (s, 6H), 2.51 (s, 6H), 3.45 (s, 6H), 3.92 (s, 6H), 5.21, 5.25 (ABq, *J* = 12.5 Hz, 4H), 5.76 (s, 2H), 5.77–5.79 (m, 2H), 6.09–6.10 (m, 2H), 6.45 (s, 2H), 7.29 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 4H), 7.39 (d, *J* = 7.2 Hz, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.4, 17.2, 35.4, 58.3, 65.3, 96.3, 108.4, 111.7, 116.4, 120.8, 125.6, 127.9, 128.2, 128.5, 128.7, 130.4, 134.6, 137.1, 142.9, 152.8, 157.4, 165.7, 166.1. HRMS-APCI (*m*/*z*): $[M + H]^+$ calcd for $C_{50}H_{49}N_6O_6Zn$, 893.3000; found, 893.2997.

General procedure 3 for the formation of tin complexes

Prodigiosene (1 eq. 0.15 mmol) was dissolved in MeOH (12 mL) (if the compound is not soluble in methanol a 1/1 mixture of methanol and DCM can be used), then Bu_2SnO or Ph_2SnO (2 eq., 0.30 mmol) was added. The reaction mixture was stirred at reflux temperature overnight. After cooling to room temperature, a saturated solution of $NaHCO_3$ (20 mL) was added and the reaction mixture was extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine, and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was quickly purified using flash chromatography (Al_2O_3 basic type III, DCM 100%).

Dibutyl tin(IV) complex 45. Obtained following the general procedure 3 as a thick purple oil (89%, 76 mg). ^1H NMR ($CDCl_3$, 500 MHz) 0.76 (t, *J* = 7.2 Hz, 6H), 0.90 (t, *J* = 7.5 Hz, 3H), 1.20–1.26 (m, 4H), 1.29–1.35 (m, 5H), 1.36–1.51 (m, 9H), 2.17 (s, 3H), 2.34 (s, 3H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.96 (s, 3H), 6.03 (s, 1H), 6.37–6.39 (m, 1H), 6.69 (d, *J* = 3.5 Hz, 1H), 6.88–6.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 10.1, 13.6, 14.3, 14.7, 22.8, 23.4, 24.7, 26.5, 27.1, 30.5, 31.9, 58.3, 91.5, 109.3, 112.7, 114.1, 126.3, 127.4, 130.0, 132.5, 134.1, 134.4, 149.6, 153.7, 166.5. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{29}H_{43}N_3O_1Sn_1$, 569.2423; found, 569.2420.

Dibutyl tin(IV) complex 46. Obtained following the general procedure 3 as a thick purple oil (82%, 28 mg). ^1H NMR ($CDCl_3$, 500 MHz) 0.76 (t, *J* = 7.2 Hz, 6H), 1.20–1.26, (m, 4H), 1.42–1.51 (m, 8H), 2.21 (s, 3H), 2.38 (s, 3H), 3.42 (s, 2H), 3.67 (s, 3H), 3.97 (s, 3H), 6.03 (s, 1H), 6.39–6.40 (m, 1H), 6.74 (s, 1H), 6.90–6.91 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 10.2, 13.6, 14.7, 23.5, 26.5, 27.0, 30.8, 52.0, 58.4, 91.8, 110.2, 113.1, 114.2, 118.5, 127.2, 130.7, 132.3, 133.7, 134.7, 148.5, 154.8, 167.2, 172.3. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{27}H_{37}N_3O_3Sn_1$, 571.1851; found, 571.1869.

Prodigiosin tin(IV) complex 50. Obtained following the general procedure 3 as a purple film (quant., 6.1 mg). ^1H NMR ($CDCl_3$, 500 MHz) 0.76 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H), 1.18–1.26 (m, 4H), 1.33–1.36 (m, 5H), 1.41–1.58 (m, 9H), 2.35 (s, 3H), 2.39 (t, J = 7.5 Hz, 2H), 3.95 (s, 3H), 6.02 (s, 1H), 6.39 (dd, J = 3.5, 2.0 Hz, 1H), 6.59 (s, 1H), 6.73 (dd, J = 3.5, 2.0 Hz. 1H), 6.79 (s, 1H), 6.91 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 13.6, 14.2, 14.6, 22.8, 23.4, 26.2, 26.5, 27.1, 30.2, 31.9, 58.4, 91.9, 110.2, 113.1, 116.9, 125.1, 127.5, 129.0, 130.6, 132.3, 135.0, 148.6, 154.9, 167.4. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{28}H_{41}N_3O_1Sn_1$, 555.2266; found, 555.2266.

Dibutyl tin(IV) complex 51. Obtained following the general procedure 3 as a thick purple oil (80%, 48 mg). ^1H NMR ($CDCl_3$, 500 MHz) 0.63 (t, J = 7.5 Hz, 6H), 1.10 (sext., J = 7.5 Hz, 4H), 1.33 (quint., J = 7.5 Hz, 4H), 1.54–1.65 (m, 4 H), 2.50 (s, 3H), 2.69 (s, 3H), 4.04 (s, 3H), 5.32 (s, 2H), 6.28 (s, 1H), 6.99–7.02 (m, 2H), 7.14–7.17 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 8.0 Hz, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.67 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.4, 13.5, 17.6, 24.3, 26.2, 27.0, 58.7, 65.6, 93.8, 103.1, 114.2, 116.7, 117.4, 118.8, 121.7, 123.0, 128.1, 128.3, 128.7, 128.9, 132.7, 134.7, 136.9, 137.5, 141.4, 144.4, 155.1, 156.6, 165.5, 168.0. HRMS-APCI (*m*/*z*): $[M + H]^+$ calcd for $C_{36}H_{42}N_3O_5$, 684.2243; found, 684.2209.

Dibutyl tin(IV) complex 52. Obtained following the general procedure 3 as a purple thick oil (87%, 53 mg). ^1H NMR ($CDCl_3$, 500 MHz) 0.63 (t, J = 7.2 Hz, 6H), 0.91 (t, J = 6.7 Hz, 3H), 1.08–1.11 (m, 4H), 1.30–1.38 (m, 7H), 1.44–1.48 (m, 3H), 1.53–1.61 (m, 4H), 2.20 (s, 3H), 2.37–2.40 (m, 5H), 4.00 (s, 3H), 6.26 (s, 1H), 6.87 (s, 1H), 6.98 (t, J = 7.5 Hz, 1H), 7.02 (s, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 10.1, 13.5, 14.2, 15.1, 22.8, 23.6, 24.7, 26.2, 27.1, 30.2, 31.9, 58.3, 92.8, 99.9, 113.8, 116.4, 118.2, 121.1, 121.6, 125.5, 129.3, 132.8, 136.1, 137.3, 138.6, 143.8, 151.4, 154.5, 165.2. UV (DCM) λ_{max} (ε): 498 nm (55 600 L mol^{-1} cm^{-1}). LRMS 620.3 $[M + H]^+$. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{33}H_{46}N_3O_1Sn_1$, 620.2657; found, 620.2683.

Parasite growth assay

Drug trials were carried out on *Plasmodium falciparum* 3D7 strain in triplicate in 24-well plates, with each well containing 2% washed red blood cells and the desired drug concentration in 2 mL of media with 0.2% parasitemia. Drugs were dissolved in DMSO prior to dilution. Parasitemia was assessed using a previously described fluorescence assay[40] modified by a reduction in the quantity of SybrGreen in the assay buffer to 0.1 μL mL^{-1} and normalization against a red blood cell only control. Fluorescence was assessed with an Ascent Fluoroscan microplate reader (Labsystems). The DSMO alone had no effect on parasite growth at the final concentrations used.

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