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ARTICLE

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 IC₅₀ 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 1950's, 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 (Figure 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 immunosuppressive¹⁰ and anticancer¹¹ properties. Although the antimalarial activity of natural prodigiosins was reported several years ago,¹² the parasitocidal 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 modifications at the A- and C-rings (Figure 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.

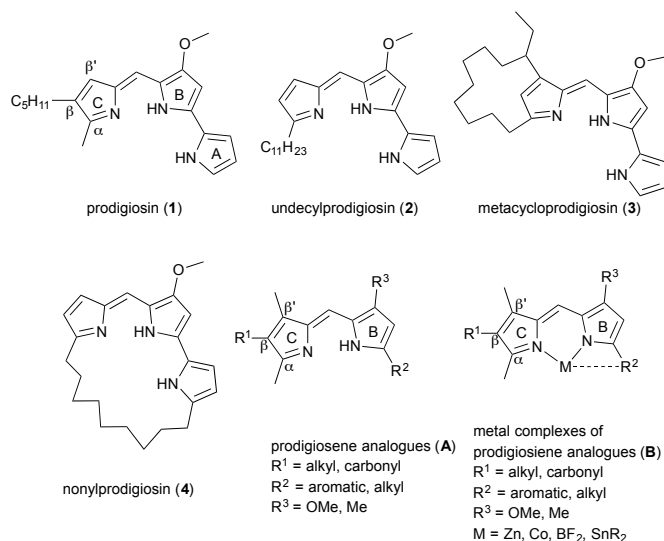


Figure 1 Selected examples of natural prodigiosins (1-4) and prodigiosene analogues (A and B).

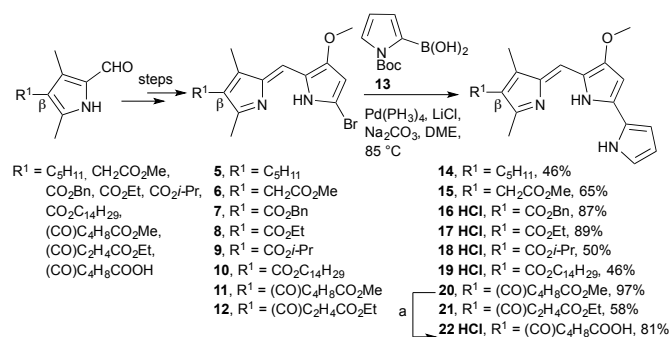
Some organometallic complexes exhibit noteworthy antimalarial properties.^{6c} For example, ferroquine is a ferrocenyl complex of chloroquine¹⁵ that was evaluated in a phase II clinical trial.¹⁶ Given this, plus the fact that tin-

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 (Figure 1, B) and discuss their complementary behaviour compared to the corresponding free-base dipyrins.

Results and discussion

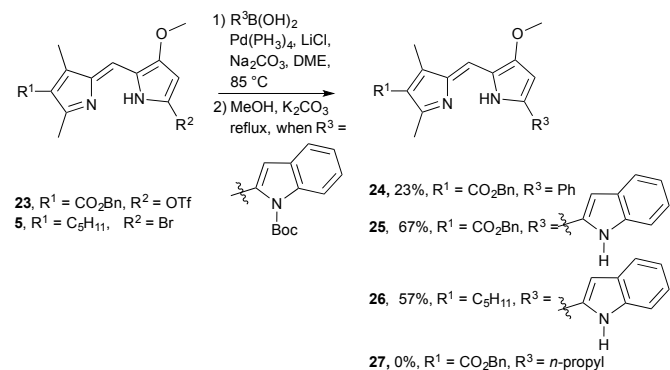
Synthesis of prodigiosenes

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.



Scheme 1 Synthesis of prodigiosenes 14-22. ^aKOH, THF/H₂O, 70 °C, then HCl

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, dipyrins **23** and **5** were subjected to Suzuki-Miyaura reaction conditions using various boronic acids (Scheme 2).

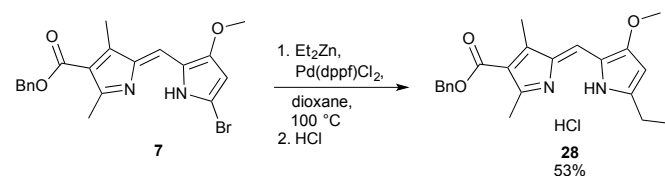


Scheme 2 Synthesis of A-ring modified prodigiosenes using a Suzuki-Miyaura coupling.

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

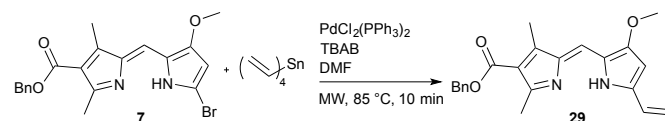
deprotection step using potassium carbonate in methanol was necessary in order to obtain compounds **25** and **26**. Unfortunately, when *n*-propyl boronic acid was used, the expected product (**27**) was not obtained even when employing reaction conditions that had been successful in coupling alkyl boronic acids and halogeno-arenes.¹⁸

We thus moved to a Negishi-type reaction¹⁹ in order to obtain a prodigiosene substituted with an alkyl group in lieu of an A-ring heterocycle: the ethyl-substituted dipyrin salt **28** was rendered in 53% yield, after quenching with HCl and a simple precipitation from methanol (Scheme 3).



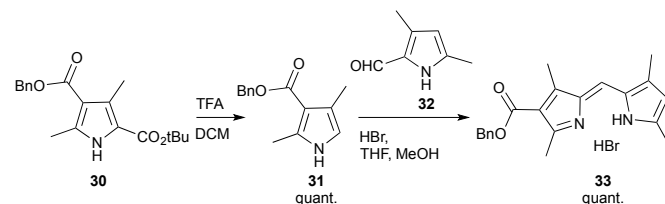
Scheme 3 Synthesis of a dipyrin substituted with an alkyl group.

To extend the conjugation of the dipyrin core we attempted a Stille coupling of tetravinyltin and dipyrin **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 dipyrin **29** decomposed within a few days. Attempts to form the HCl salt of **29**, usually a stabilisation strategy for dipyrins, also failed.



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

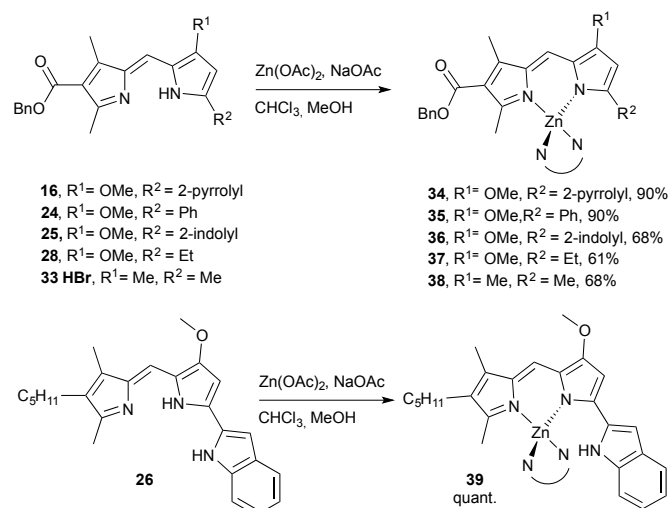
An analogue of dipyrin **28** (Scheme 3), without the B-ring methoxy substituent and bearing a methyl group in place of the ethyl substituent, was also prepared (Scheme 5, **33**). This was obtained via deprotection and decarboxylation of pyrrole **30**^{17a} to quantitatively give the α -free pyrrole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



Scheme 5 Synthesis of dipyrin **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 dipyrin extended with a pyrrolyl substituent, and are thus good candidates for metal complexation.²² Indeed both nitrogen atoms of the dipyrin moiety could be involved in chelation to the metal centre. Alternatively the three nitrogen atoms of the entire dipyrinato-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 complex²⁴ proposed to be partially responsible for the anticancer properties of prodigiosin.²⁵ Several homoleptic zinc complexes, MP₂, of our prodigiosenes (P) were thus prepared (Scheme 6).²⁶

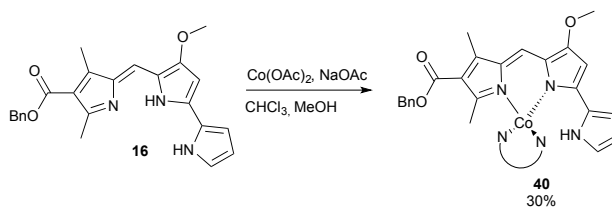


Scheme 6 Synthesis of zinc complexes of prodigiosenes and dipyrins.

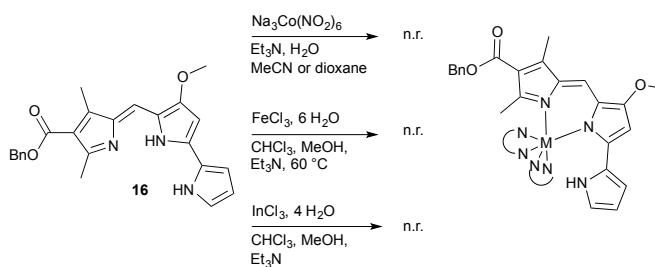
C-ring benzyl ester prodigiosenes with non-modified (**16**) and modified A-rings (**24**, **25**, **28**, **33**) were obtained as their zinc-complexes (**34–38**) in moderate-to-good yields. Complex **39** with an alkyl chain in the C-ring β -position, was obtained quantitatively using the same conditions. As expected, and in keeping with previous work involving dipyrins and prodigiosenes,^{24, 27} all zinc complexes were obtained as single discrete ZnP₂ complexes, with no mass spectral evidence to the contrary.

Dipyrins 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) (MP₂, **40**) was obtained in 30% yield using benzyl ester prodigiosene **16** as starting material. Surprisingly, although dipyrins 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

Formation of metal(II) complexes:

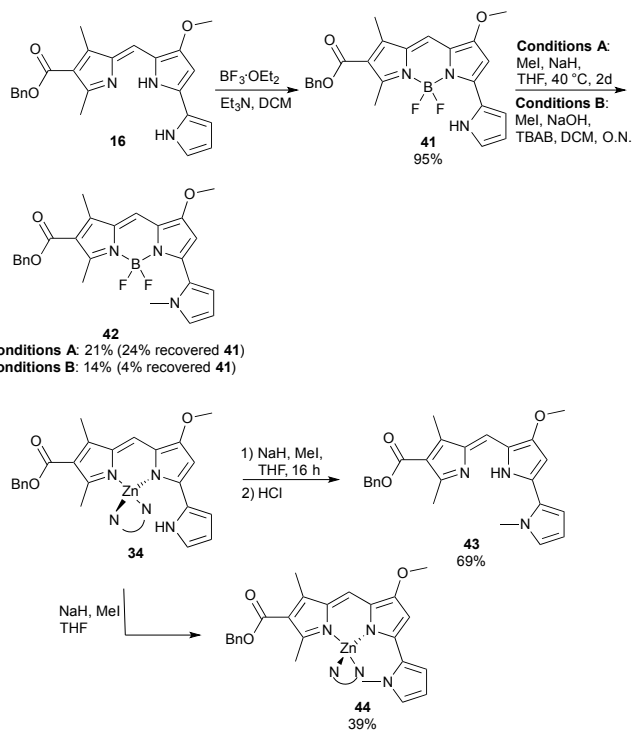


Attempted formation of metal(III) complexes:



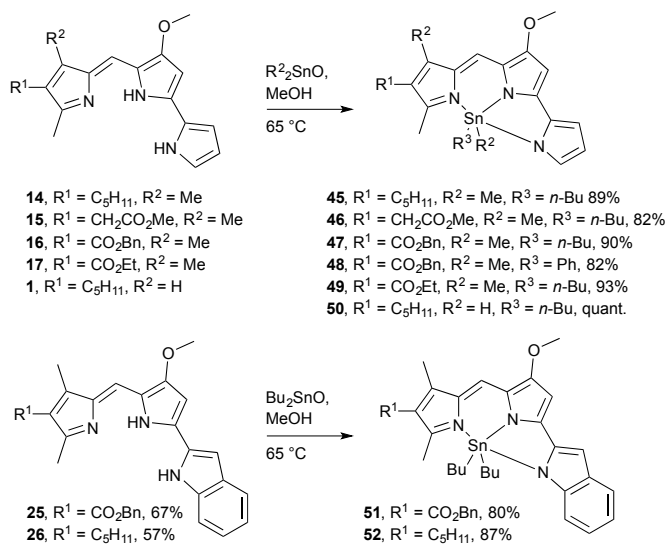
Scheme 7 Metal complexes of prodigiosenes; n.r. = no reaction.

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 dipyrinato unit of prodigiosene **16** was protected (Scheme 8).^{31,32}



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

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 DCM³³ 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).



Scheme 9 Preparation of tin complexes of prodigiosenes.

We have previously reported that prodigiosene tin complexes **47** and **48** (Scheme 9) exhibit a low acute systemic 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 Bu₂SnO and Ph₂SnO.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 (IC₅₀). So as to facilitate discussion of valuable activity levels, efficient antimalarial activity can be appreciated as excellent (IC₅₀ < 1 μM) and good (1 μM < IC₅₀ < 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 IC₅₀ 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 IC₅₀ values (116 nM and 521 nM, respectively) compared to their corresponding free-base prodigiosenes **16** and **17** (IC₅₀ = 0.9 μM and 1.5 μM, respectively) but the cobalt-prodigiosene dimer (CoP₂, where P = prodigiosene, **40**), the diphenyl tin complex (**48**), the zinc dimer (ZnP₂, **34**) and BF₂ (**41**) complexes were not as effective as their free-base ligand (**16**).

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

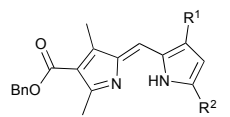
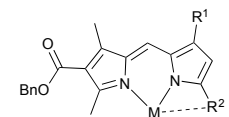
R	IC ₅₀ (free-base)	M	IC ₅₀ (complex)
chloroquine	15 nM		
prodigiosin	11 nM (1)		
-benzyl	0.9 μM (16)	SnBu ₂	116 nM (47)
-benzyl		Co ^a	5 < IC ₅₀ < 50 μM (40)
-benzyl		SnPh ₂	5 < IC ₅₀ < 50 μM (48)
-benzyl		Zn ^a	≈ 50 μM (34)
-benzyl		BF ₂ ^b	No effect (41)
-ethyl	1.5 μM (17)	SnBu ₂	521 nM (49)
-i-propyl	1.0 μM (18)		
-C ₁₄ H ₂₈	No effect (19)		

^aThe Co and Zn complexes are dimeric, i.e. MP₂ where P = prodigiosene with chelating dipyrinato units and uncomplexed N-H moieties on the A-ring pyrroles; ^bFor the BF₂ complex the dipyrinato unit complexes with boron leaving an uncomplexed N-H on the A-ring pyrrole

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 pyrrole for parasitocidal activity while substituents at α- and β'-positions of the C-ring can be varied.¹⁴ For this purpose we compared the IC₅₀ values of several benzyl ester prodigiosenes substituted with various R² 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**

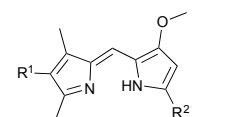
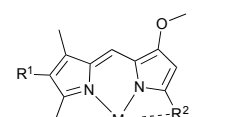
(compare IC_{50} of 938 nM for **16** vs. $5 > IC_{50} > 50 \mu M$ for **43**) showing that the presence of the N–H moiety of the A-ring is essential. This is supported by the moderate IC_{50} values of prodigiosenes substituted with a phenyl (**24**) or ethyl group (**28**). Replacement of the A-ring pyrrole with an indole slightly decreases the antimalarial activity (Compare $IC_{50} = 0.9 \mu M$ for **16** and $IC_{50} = 5.6 \mu M$ 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**).

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

				
R ¹	R ²	IC_{50} (free-base)	M	IC_{50} (complex)
		11 nM (1)		
-OMe	-2-pyrrolyl	0.9 μM (16)		
-OMe	-1-Me-2-pyrrolyl	$5 < IC_{50} < 50 \mu M$ (43)	Zn ^a	$\approx 50 \mu M$ (44)
-OMe	-phenyl	$5 < IC_{50} < 50 \mu M$ (24)	Zn ^a	No effect (35)
-OMe	-ethyl	$5 < IC_{50} < 50 \mu M$ (28)	Zn ^a	No effect (37)
-OMe	-2-indolyl	5.6 μM (25)	SnBu ₂	4.7 μM (51)
-OMe	-2-indolyl		Zn ^a	$\approx 50 \mu M$ (36)
-Me	-Me	4.7 μM (33)	Zn ^a	No effect (38)

^aThe Zn complexes are dimeric, i.e. MP₂ where P = prodigiosene with chelating dipyrinato 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)
		11 nM (1)		
-C ₃ H ₁₁	2-pyrrolyl	19 nM (14)	SnBu ₂	7.1 nM (50)
-C ₃ H ₁₁	2-indolyl	98 nM (26)	SnBu ₂	18 nM (45)
-C ₃ H ₁₁	2-indolyl		SnBu ₂	1.4 μM (52)
-CH ₂ CO ₂ Me	2-pyrrolyl	1.5 μM (15)	Zn ^a	$5 < IC_{50} < 50 \mu M$ (39)
-(CO)C ₄ H ₈ CO ₂ Me	2-pyrrolyl	$5 < IC_{50} < 50$ (20)	SnBu ₂	56 nM (46)
-(CO)C ₃ H ₄ CO ₂ Et	2-pyrrolyl	$5 < IC_{50} < 50$ (21)		
-(CO)C ₄ H ₈ CO ₂ H	2-pyrrolyl	$\approx 50 \mu M$ (22)		

^aThe Zn complex is dimeric, i.e. MP₂ where P = prodigiosene with a chelating dipyrinato unit and an uncomplexed N–H moiety on the A-ring pyrrole.

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 (Figure 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** 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 $IC_{50} > 5 \mu M$). 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 SI). 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^7 -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^7 -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 excellent³⁶ 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, BF₂ 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 CDCl₃ 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 ¹³C 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 Tf₂O (2.7 mL, 15.9 mmol). After 4 h stirring at this temperature, the reaction was quenched with sat. aqueous NaHCO₃ (400 mL), then extracted with DCM (3 x 200 mL). The combined organic layers were washed with brine, and then dried (Na₂SO₄). After evaporation of the solvents under reduced pressure, the crude material was purified using flash column chromatography (SiO₂, EtOAc/hexane 2/8) to give a yellow solid (1.5 g, 55%). ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₂₁H₂₀F₃N₂O₆S₁, 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 N₂, and then palladium tetrakis(PPh₃) (56 mg, 10 mol/%) was added. Then a degassed 2 M solution of Na₂CO₃ 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 (Na₂SO₄).

(Z)-Benzyl 2-((3-methoxy-5-phenyl-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate 24: Obtained following general procedure 1 and then purification using chromatography (Al₂O₃ basic type III, EtOAc/hexane 1/9) as an orange solid (23%, 62 mg). Mp 169 °C. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₂₆H₂₅N₂O₃, 413.1860; found, 413.1864.

(Z)-Benzyl 2-((5-(1H-indol-2-yl)-3-methoxy-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrole-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 K₂CO₃ (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 (Na₂SO₄). After evaporation of the solvent under reduced pressure the crude product was purified using column chromatography (Al₂O₃ type III basic, EtOAc/hexanes 2/8) to give a red solid (67%, 203 mg). Mp 113 °C. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₂₈H₂₆N₃O₃, 452.1969; found, 451.1967.

(Z)-2-(5-((3,5-Dimethyl-4-pentyl-2H-pyrrol-2-ylidene)methyl)-4-methoxy-1H-pyrrol-2-yl)-1H-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 K₂CO₃ (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 (Na₂SO₄). After evaporation of the solvent under reduced pressure the crude was purified using column chromatography (Al₂O₃ type III basic, EtOAc/hexanes 1/9) to give a red glass (57%, 94 mg). ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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

¹.cm⁻¹). HRMS-ESI (*m/z*): [M+H]⁺ calcd for C₂₅H₃₀N₃O₁, 388.2383; found, 388.2377.

(Z)-Benzyl 2-((5-ethyl-3-methoxy-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate hydrochloride 28: Under nitrogen to a Shlenk tube containing (Z)-benzyl 2-((5-bromo-3-methoxy-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate **7** (200 mg, 0.48 mmol) and Pd(dppf)Cl₂ (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 Et₂Zn (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 (Na₂SO₄). 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. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₂₂H₂₅N₂O₃, 365.1860; found, 365.1868.

(Z)-Benzyl 2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate hydrobromide 33: To a mixture of THF/MeOH (1.6/1.6 mL) was added benzyl 2,4-dimethyl-1H-pyrrole-3-carboxylate **31** (372 mg, 1.62 mmol) and 3,5-dimethyl-1H-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 Et₂O (3 × 15 mL) to give the product as a yellow solid (300 mg, quant.) Mp 226 °C. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₂₁H₂₃N₂O₂, 335.1754; found, 335.1746.

General procedure 2 for the synthesis of Zn complexes: To a solution of prodigiosene (1 eq.) in CHCl₃ (0.04M) was added a solution of Zn(OAc)₂·2H₂O (2.4 eq.) and NaOAc·3H₂O (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 (Na₂SO₄).

Prodigiosene zinc(II) complex 35: Obtained following general procedure 2 then, after concentration, the residue was purified using flash chromatography (Al₂O₃ III basic, EtOAc/hexane 1/9 then 2/8) to give a red solid (48 mg, 90%). Mp 181 °C. ¹H NMR (CDCl₃, 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): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{52}\text{H}_{46}\text{N}_4\text{O}_6\text{Zn}$, 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): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{56}\text{H}_{49}\text{N}_6\text{O}_6\text{Zn}$, 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): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{44}\text{H}_{47}\text{N}_4\text{O}_6\text{Zn}$, 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): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{42}\text{H}_{43}\text{N}_4\text{O}_4\text{Zn}$, 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 $[\text{M}+\text{H}]^+$.

HRMS-APCI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{50}\text{H}_{57}\text{N}_6\text{O}_2\text{Zn}$, 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 $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (77 mg, 0.31 mmol) and $\text{NaOAc} \cdot 3\text{H}_2\text{O}$ (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): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{48}\text{H}_{45}\text{CoN}_6\text{O}_6$, 860.2727; found, 860.2697.

2-((Benzyloxy)carbonyl)-5,5-difluoro-9-methoxy-1,3-dimethyl-7-(1H-pyrrol-2-yl)-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide 41:

The HCl salt of prodigiosene **16** (300mg, 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 $\text{BF}_3 \cdot \text{OEt}_2$ (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): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{22}\text{BF}_2\text{N}_3\text{O}_3$, 449.1717; found, 449.1705.

2-((Benzyloxy)carbonyl)-5,5-difluoro-9-methoxy-1,3-dimethyl-7-(1-methyl-1H-pyrrol-2-yl)-5H-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 μ L, 12 eq). The reaction mixture was heated at 40 $^{\circ}$ 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 \times 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 $^{\circ}$ 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): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{24}\text{B}_1\text{F}_2\text{N}_3\text{Na}_1\text{O}_1$, 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 $^{\circ}$ C. After 30 min stirring at room temperature, MeI (11 μ L, 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 \times 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): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_3$, 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 $^{\circ}$ C. After 30 min stirring at room temperature, MeI (14 μ L, 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 \times 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): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{50}\text{H}_{49}\text{N}_6\text{O}_6\text{Zn}$, 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 \times 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): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{43}\text{N}_3\text{O}_1\text{Sn}_1$, 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): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{37}\text{N}_3\text{O}_3\text{Sn}_1$, 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): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{41}\text{N}_3\text{O}_1\text{Sn}_1$, 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 assay⁴⁰ modified by a reduction in the quantity of SybrGreen in the assay buffer to 0.1 μ L/mL and normalization against a red blood cell only control. Fluorescence was assessed with an Ascent Fluoroscan microplate reader (Labsystems). The DMSO alone had no effect on parasite growth at the final concentrations used.

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