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 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 immunosuppressive10 and anticancer11 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-

†Electronic supplementary information (ESI) available: General procedures for antimalarial assays, growth and isolation of prodigiosin, plus spectral characterisation data for all new compounds. See DOI: 10.1039/c3ob42548g
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 carboxyl 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 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,9 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),27 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 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 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 3022 to quantitatively give the α-free pyrrole 31. Then, condensation with aldehyde 3221 gave the dipyrrin 33 in excellent yield.
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. 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. Indeed both nitrogen atoms of the dipyrrin moiety could be involved in chelation to the metal centre. Alternatively the three nitrogen atoms of the dipyrrinato-pyrrolyl skeleton could all be coordinated. Homoleptic dimeric zinc complexes of prodigiosenes, and the natural compound are known, as is an oxidised Cu(II):prodigiosin complex proposed to be partially responsible for the anticancer properties of prodigiosin. Several homoleptic zinc complexes, MP₄, of our prodigiosenes (P) were thus prepared (Scheme 6).

C-ring benzyl ester prodigiosenes with non-modified (16) and modified A-rings (24, 25, 28, 33) were obtained as their zinc-complexes 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, all zinc complexes were obtained as single discrete ZnP₂ complexes, with no mass spectral evidence to the contrary.

Dipyrrins form complexes with numerous M(II) and M(III) metals. 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, a complex of cobalt(II) (MP₂, 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), Fe(III) and In(III) failed in our hands, perhaps due to steric hindrance at the C-ring α-position (Scheme 7).

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).

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 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 toxicity profile, providing a promising platform for further investigation.
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$_2$SnO and Ph$_2$SnO. 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),\(^{16}\) 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

<table>
<thead>
<tr>
<th>R</th>
<th>IC$_{50}$ (free-base)</th>
<th>M</th>
<th>IC$_{50}$ (complex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>15 nM</td>
<td></td>
<td>15 nM (1)</td>
</tr>
<tr>
<td>Prodigiosin</td>
<td>11 nM (1)</td>
<td></td>
<td>0.9 μM (16)</td>
</tr>
<tr>
<td>-Benzyl</td>
<td></td>
<td></td>
<td>1.5 μM (17)</td>
</tr>
<tr>
<td>-C$<em>4$H$</em>{10}$</td>
<td></td>
<td></td>
<td>1.0 μM (18)</td>
</tr>
<tr>
<td>-C$<em>4$H$</em>{10}$</td>
<td></td>
<td></td>
<td>No effect (19)</td>
</tr>
<tr>
<td>SnBu$_2$</td>
<td>116 nM (47)</td>
<td></td>
<td>116 nM (47)</td>
</tr>
<tr>
<td>Co</td>
<td></td>
<td></td>
<td>5 &lt; IC$_{50}$ &lt; 50 μM (40)</td>
</tr>
<tr>
<td>SnH$_2$</td>
<td>5 &lt; IC$_{50}$ &lt; 50 μM (48)</td>
<td></td>
<td>5 &lt; IC$_{50}$ &lt; 50 μM (48)</td>
</tr>
<tr>
<td>Zn$^{a}$</td>
<td>≈50 μM (34)</td>
<td></td>
<td>≈50 μM (34)</td>
</tr>
<tr>
<td>BF$_2$$^{b}$</td>
<td>No effect (41)</td>
<td></td>
<td>No effect (41)</td>
</tr>
<tr>
<td>SnBu$_2$</td>
<td>521 nM (49)</td>
<td></td>
<td>521 nM (49)</td>
</tr>
</tbody>
</table>

$^a$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.

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

**Scheme 9** Preparation of tin complexes of prodigiosenes.
pyrrole for parasiticidal activity while substituents at α- and β-positions of the C-ring can be varied.\textsuperscript{14} For this purpose we compared the IC\textsubscript{50} values of several benzyl ester prodigiosenes substituted with various R\textsuperscript{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\textsubscript{50} of 938 nM for 16 vs. 5 > IC\textsubscript{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\textsubscript{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\textsubscript{50} = 0.9 μM for 16 and IC\textsubscript{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\textsubscript{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,\textsuperscript{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,\textsuperscript{17} and that analogue 14 possesses similar properties to the natural compound (i.e., anticancer, transmembrane anion transport and DNA cleavage activity).\textsuperscript{17b} Here, compound 14 exhibits an excellent IC\textsubscript{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\textsubscript{50} = 19 nM for 14 and IC\textsubscript{50} 98 nM for 26). For prodigiosin 1

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

<table>
<thead>
<tr>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>IC\textsubscript{50} (free-base)</th>
<th>M</th>
<th>IC\textsubscript{50} (complex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodigiosin</td>
<td>-OMe</td>
<td>11 nM (1)</td>
<td>Sn\textsuperscript{a}</td>
<td>≈50 μM (44)</td>
</tr>
<tr>
<td></td>
<td>-2-Pyrrolyl</td>
<td>0.9 μM (16)</td>
<td>Zn\textsuperscript{a}</td>
<td>≈50 μM (44)</td>
</tr>
<tr>
<td></td>
<td>-1-Me-2-pyrrolyl</td>
<td>5 &lt; IC\textsubscript{50} &lt; 50 μM (43)</td>
<td>Zn\textsuperscript{a}</td>
<td>No effect (35)</td>
</tr>
<tr>
<td></td>
<td>-Phenyl</td>
<td>5 &lt; IC\textsubscript{50} &lt; 50 μM (24)</td>
<td>Zn\textsuperscript{a}</td>
<td>No effect (37)</td>
</tr>
<tr>
<td></td>
<td>-Ethyl</td>
<td>5 &lt; IC\textsubscript{50} &lt; 50 μM (28)</td>
<td>Zn\textsuperscript{a}</td>
<td>No effect (37)</td>
</tr>
<tr>
<td></td>
<td>-2-Indolyl</td>
<td>5.6 μM (25)</td>
<td>SnBu\textsubscript{2}</td>
<td>4.7 μM (51)</td>
</tr>
<tr>
<td></td>
<td>-Me</td>
<td>4.7 μM (33)</td>
<td>Zn\textsuperscript{a}</td>
<td>≈50 μM (36)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The Zn complexes are dimeric, i.e. MP\textsubscript{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

<table>
<thead>
<tr>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>IC\textsubscript{50} (free-base)</th>
<th>M</th>
<th>IC\textsubscript{50} (complex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodigiosin</td>
<td>-C\textsubscript{3}H\textsubscript{11}</td>
<td>11 nM (1)</td>
<td>SnBu\textsubscript{2}</td>
<td>7.1 nM (50)</td>
</tr>
<tr>
<td></td>
<td>2-Pyrrolyl</td>
<td>19 nM (14)</td>
<td>SnBu\textsubscript{2}</td>
<td>18 nM (45)</td>
</tr>
<tr>
<td></td>
<td>2-Indolyl</td>
<td>98 nM (26)</td>
<td>SnBu\textsubscript{2}</td>
<td>1.4 μM (52)</td>
</tr>
<tr>
<td></td>
<td>-C\textsubscript{2}H\textsubscript{11}</td>
<td>1.5 μM (15)</td>
<td>Zn\textsuperscript{a}</td>
<td>5 &lt; IC\textsubscript{50} &lt; 50 μM (39)</td>
</tr>
<tr>
<td></td>
<td>2-Indolyl</td>
<td>1.5 μM (15)</td>
<td>SnBu\textsubscript{2}</td>
<td>56 nM (46)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The Zn complex is dimeric, i.e. MP\textsubscript{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,14 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).17 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 ES1†). 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 activity against 3D7. This compound previously showed similar anticancer properties to prodigiosin 117b 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,26 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 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 31,17b 32,34 34,12b 47–4914 were prepared according to literature procedures.

(Z)-Benzy 2-(3-methoxy-5-((trifluorometyl)sulfonyloxy)-1H-pyrrol-2-yl)methylene)-3,5-dimethyl-2H-pyrrrole-4-carboxylate 23. To a suspension of (Z)-benzyl 5-(3-methoxy-5-oxo-1H-pyrrol-2(5H)-yldene)methyl)-2,4-dimethyl-1H-pyrrrole-3-carboxy-
late (2.0 g, 5.67 mmol), in dry DCM (300 mL) at 0 °C was slowly added TFE (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 × 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 (1.3 g, 55%). ¹H NMR (CDCl₃, 500 MHz) 2.24 (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, 128.8, 128.7, 133.5, 135.4, 136.6, 145.0, 161.9, 164.9, 168.2. HRMS-ESI (m/z): [M + H⁺] calcd for C₆₂H₆₂N₆O₁₃, 452.1696; found, 451.1967.

(Z)-2-(5-(3,5-Dimethyl-1H-pyrrole-2-ylidene)methyl)-4-methoxy-1H-pyrrole-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 solvents 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) λₘₚₑₜₑₐ (%) = 578 nm (118 000 L mol⁻¹ cm⁻¹). HRMS-ESI (m/z): [M + H⁺] calcd for C₂₃H₂₄N₉O₃, 388.2383; found, 388.2377.

(Z)-Benzyl 2-(5-ethyl-3-methoxy-1H-pyrrole-2-yl)-methylene)-3,5-dimethyl-2H-pyrrole-4-carboxylate 28. Under nitrogen to a Schlenk tube containing (Z)-benzyl 2-(5-bromo-3-methoxy-1H-pyrrole-2-yl)benzyl 2,4-benzylidene)-4-methoxy-1H-pyrrole-2-carbaldehyde (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 C₂₃H₂₄N₉O₃Cl, 365.1860; found, 365.1868.

(Z)-Benzyl 2-(3-(5,3-Dimethyl-1H-pyrrole-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-carboxylic acid 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), 5.52 (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, 66.8, 117.8, 119.4, 121.3, 125.0, 128.4, 128.5, 128.8, 135.9, 147.3, 149.2, 156.4, 160.5, 163.5. HRMS-APCI (m/z): [M + Br]⁺ calcd for C₃₁H₂₃N₂O₃, 335.1754; found, 335.1746.

General procedure 2 for the synthesis of Zn complexes

To a solution of prodigiosine (1 eq.) in CHCl₃ (0.04 M) 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).

**Prodigiosine zinc(II) complex 37.** 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 162 °C. ¹H NMR (CDCl₃, 500 MHz) 2.12 (s, 6H), 2.53 (s, 6H), 4.00 (s, 6H), 5.32 (s, 2H), 6.23 (s, 1H), 7.24 (s, 1H), 7.34 (m, 4H), 7.39 (m, 6H), 7.38 (m, 2H), 7.30 (m, 6H), 7.37 (m, 4H), 7.42 (m, 5H), 13.24 (br s, 1H), 13.58 (br s, 1H). ¹³C NMR (CDCl₃, 125 MHz) 12.0, 12.4, 16.8, 17.7, 65.4, 116.6, 119.4, 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 C₄₄H₄₇N₄O₆Zn, 731.2570; found, 731.2577.

**Zinc(u) 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 (CDCl₃, 500 MHz) 1.93 (s, 6H), 2.19 (s, 6H), 2.33 (s, 6H), 2.55 (s, 6H), 6.08 (s, 2H), 7.16 (s, 2H), 7.27−7.30 (m, 2H), 7.34 (t, J = 7.2 Hz, 4H), 7.40 (d, J = 7.2 Hz, 4H). ¹³C NMR (CDCl₃, 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 C₄₄H₄₇N₄O₆Zn, 731.2570; found, 731.2577.

**Zinc(u) complex 39.** Obtained following general procedure 2 then, after concentration, the residue was purified using column chromatography (Al₂O₃ type III basic, DCM–hexanes 3/7) to give a red film (55 mg, quant.). ¹H NMR (CDCl₃, 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, 2H). ¹³C NMR (CDCl₃, 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, 133.7, 133.8, 145.8, 158.2, 163.9. LRMS 837.3 [M + H]⁺; HRMS-APCI (m/z): [M + H]⁺ calcd for C₅₀H₅₇N₆O₂Zn, 837.3829; found, 837.3818.

**Prodigiosine cobalt(u) complex 40.** To a solution of prodigiosine 16 (50 mg, 0.12 mmol) in CHCl₃ (12 mL) was added a solution of Co(OAc)₂·4H₂O (77 mg, 0.31 mmol) and NaOAc·3H₂O (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 (Na₂SO₄). After concentration under vacuum the residue was purified using flash chromatography (Al₂O₃ 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 C₅₀H₅₇N₆O₂Co, 860.2727; found, 860.2697.

2-(Benzoylcarbonyl)-5,5-difluoro-9-methoxy-1,3-dimethyl-7-(1H-pyrrol-2-yl)-3H-dipyrrrolo[1,2-c:1',2'-f][1,3]diazaborinin-4-ium-5-uide 41. The HCl salt of prodigiosine 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 BF₃·OEt₂ (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 (Na₂SO₄). After evaporation of the solvent the crude material was purified using flash column chromatography (Al₂O₃ 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 (CDCl₃, 500 MHz) 2.42 (s, 3H), 2.80 (s, 3H), 3.99 (s, 6H), 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). ¹³C NMR...
7.2 Hz, 1H), 7.38 (t, 6.71 μm) acetate (3 × 20 mL). The combined organic layers were 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 (Na2SO4). After evaporation of the solvent under reduced pressure the crude product was purified using column chromatography (Al2O3 type III basic, EtOAc–hexanes 3/7) to give a dark pink solid (21%, 11 mg).

Method B: to a solution of prodigiosine 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 (50 mL) then dried (Na2SO4). After evaporation of the solvent under reduced pressure the crude material was purified using column chromatography (Al2O3 type III basic, EtOAc–hexanes 3/7) to give a dark pink solid (14%, 11 mg). Mp 203 °C. 1H NMR (CDCl3, 500 MHz) 0.76 (t, 1.51 (m, 8H), 2.21 (s, 3H), 2.38 (s, 3H), 3.42 (s, 2H), 3.67 (m, 1H), 6.69 (d, J = 7.2 Hz, 2H). 13C NMR (CDCl3, 125 MHz) 11.6, 13.6, 21.4, 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-APCI (m/z): [M + Na] + calcd for C25H26N3O3, 416.1771; found, 416.1758.

(Z)-Benzyl 2-[(4-methoxy-1'-methyl-1H,1'H-[2,2'-bipyridyl]-5-yl)methylene]-3,5-dimethyl-2H-pyrrrole-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 prodigiosine 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 (Na2SO4). After evaporation of the solvent under reduced pressure the crude material was purified using column chromatography (Al2O3 type III basic, EtOAc–hexanes 4/6) to give a dark red film (39%, 29 mg). 1H NMR (CDCl3, 500 MHz) 2.10 (s, 3H), 2.51 (s, 6H), 3.45 (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 (d, J = 7.2 Hz, 4H). 13C NMR (CDCl3, 125 MHz) 12.1, 13.6, 58.7, 65.4, 97.0, 110.8, 111.7, 112.8, 113.5, 115.5, 127.5, 128.0, 128.2, 128.6, 128.9, 136.7, 141.3, 142.9, 160.0, 165.6, 167.3 (1 carbon non accounted for). HRMS-ESI (m/z): [M + H] + calcd for C22H24N3O4, 416.1969; found, 416.1984.

Prodigiosene zinc(u) complex 44. To a suspension of NaH (60% in grease, 9 mg, 0.23 mmol) in anhydrous THF (4 mL) under nitrogen was added prodigiosine 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 (Na2SO4). After evaporation of the solvent under reduced pressure the crude material was purified using column chromatography (Al2O3 type III basic, EtOAc–hexanes 4/6) to give a dark red film (39%, 29 mg). 1H NMR (CDCl3, 500 MHz) 2.10 (s, 3H), 2.51 (s, 6H), 3.45 (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 (d, J = 7.2 Hz, 4H). 13C NMR (CDCl3, 125 MHz) 12.1, 13.6, 58.7, 65.4, 97.0, 110.8, 111.7, 112.8, 113.5, 115.5, 127.5, 128.0, 128.2, 128.6, 128.9, 136.7, 141.3, 142.9, 160.0, 165.6, 167.3 (1 carbon non accounted for). HRMS-ESI (m/z): [M + H] + calcd for C22H24N3O4, 416.1969; found, 416.1984.

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 (Na2SO4). After evaporation of the solvent under reduced pressure the crude product was purified using column chromatography (Al2O3 type III basic, EtOAc–hexanes 3/7) to give a dark pink solid (21%, 11 mg).

Method B: to a solution of prodigiosine 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 (50 mL) then dried (Na2SO4). After evaporation of the solvent under reduced pressure the crude material was purified using column chromatography (Al2O3 type III basic, EtOAc–hexanes 3/7) to give a dark pink solid (14%, 11 mg). Mp 203 °C. 1H NMR (CDCl3, 500 MHz) 0.76 (s, 3H), 2.77 (s, 3H), 3.77 (s, 3H), 3.91 (s, 3H), 5.10 (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). 13C NMR (CDCl3, 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, 134.6, 139.6, 151.4, 155.8, 164.2, 164.9. HRMS-ESI (m/z): [M + Na] + calcd for C25H24B1F2N3Na1O1, 486.1771; found, 486.1758.
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]) calcd for C_{25}H_{32}N_{3}O_{5}S_{1}, 571.1851; found, 571.1869.

**Prodigiosin tin(v) complex 50.** Obtained following the general procedure 3 as a purple film (quant., 6.1 mg). ¹H NMR (CDCl₃, 500 MHz) 0.63 (t, J = 7.2 Hz, 6H), 1.08 (s, 3H), 1.33 (quint., 1H), 1.58–1.65 (m, 9H), 1.70 (t, J = 7.5 Hz, 6H), 2.50 (s, 3H), 6.28 (s, 1H), 6.59 (s, 1H), 6.73 (dd, J = 3.5, 2.0 Hz, 1H), 6.79 (s, 1H), 6.91 (s, 1H). ¹³C NMR (CDCl₃, 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_{36}H_{42}N_{3}O_{5}S_{1}, 620.2657; found, 620.2643.

**Dibutyl tin(v) complex 51.** Obtained following the general procedure 3 as a thick purple oil (quant., 6.1 mg). ¹H NMR (CDCl₃, 500 MHz) 0.63 (t, J = 7.2 Hz, 6H), 1.08 (s, 3H), 1.33 (quint., 1H), 1.58–1.65 (m, 9H), 1.70 (t, J = 7.5 Hz, 6H), 2.50 (s, 3H), 6.28 (s, 1H), 6.59 (s, 1H), 6.73 (dd, J = 3.5, 2.0 Hz, 1H), 6.79 (s, 1H), 6.91 (s, 1H). ¹³C NMR (CDCl₃, 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_{36}H_{42}N_{3}O_{5}S_{1}, 620.2657; found, 620.2643.

**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 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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**Notes and references**


