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Review

Ferrocene–indole hybrids for cancer and malaria therapy

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ABSTRACT

We report the synthesis, characterization, and cytotoxic and antimalarial activity of ferrocene–indole hybrids **8**–**14**. The 2-phenylindole scaffold was chosen because of its potent antimitotic activity and ferrocene was chosen following the development of ferrocifens, ferrocene derivatives of tamoxifen, which are prototypes of a new family of organometallic anti-estrogens. Ferrocene–indole hybrids **8**–**14** and their corresponding organic analogues **1**–**7** showed only moderate antimalarial activities, while ferrocene–indole hybrids **11** and **12** showed excellent *in vitro* activities against the A549 human carcinoma cell line, with IC_{50} values of 5 and 7 μM respectively. These ferrocene–indole hybrids were up to 25-fold more potent as cytotoxic agents than their purely organic analogues.

Contents

1. Introduction 1012
2. Results and discussion 1013
 2.1. Chemistry 1013
 2.2. Biology 1013
  2.2.1. Cytotoxic activities 1013
  2.2.2. Antimalarial activities 1013
3. Conclusion 1014
4. Experimental 1014
 4.1. Chemistry 1014
  4.1.1. Full description of ^{1}H, ^{19}F and ^{13}C NMR spectra for 2-pheylylindoles (**1**–**7**) [19] 1014
   4.1.1.1. 2-Phenyl-1H-indole (**1**) 1014
   4.1.1.2. 2-(4-Chlorophenyl)-1H-indole (**2**) 1014
   4.1.1.3. 2-(4-Fluorophenyl)-1H-indole (**3**) 1014
   4.1.1.4. 5-Methoxy-2-phenyl-1H-indole (**4**) 1014
   4.1.1.5. 5-Nitro-2-phenyl-1H-indole (**5**) 1015

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4.1.1.6. 5-Chloro-2-phenyl-1H-indole (**6**) 1015
4.1.1.7. 2-(2pyiridyl)-1H-indole (**7**) 1015
4.1.2. General synthetic procedure for the preparation of 3-ferrocenylmethyl-2-pheylindoles (**8**–**14**) 1015
4.1.2.1. 3-Ferrocenylmethyl-2-phenyl-1H-indole (**8**) 1015
4.1.2.2. 2-(4-Chlorophenyl)-3-ferrocenylmethyl-1H-indole (**9**) 1015
4.1.2.3. 3-Ferrocenylmethyl-2-(4-fluorophenyl)-1H-indole (**10**) 1015
4.1.2.4. 3-Ferrocenylmethyl-5-methoxy-2-phenyl-1H-indole (**11**) 1015
4.1.2.5. 3-Ferrocenylmethyl-5-nitro-2-phenyl-1H-indole (**12**) 1015
4.1.2.6. 5-Chloro-3-ferrocenylmethyl-2-phenyl-1H-indole (**13**) 1015
4.1.2.7. 3-Ferrocenylmethyl-2-(2pyridyl)-1H-indole (**14**) 1016
4.2. Biology 1016
4.2.1. Cell culture 1016
4.2.2. Cell proliferation assay 1016
4.2.3. Antiplasmodial assay 1016
Acknowledgment 1016
References 1016

1. Introduction

Organometallic medicinal chemistry is the most promising branch of bioorganometallic chemistry [1]. Pioneered by the group of Paul Dyson [2], an extensive series of ruthenium–arene complexes have shown selective effects on metastasis. Moreover, the group of Eric Meggers [3] developed ruthenium–cyclopentadienyl half-sandwich compounds based on the structure of staurosporine that proved to be very effective kinase inhibitors. Thanks to its unique properties such as aromaticity, aqueous stability, and redox behaviour [4], ferrocene is increasingly used in the development of new anticancer drugs [5]. Impressive results have been obtained by the group of Gérard Jaouen [6], with the development of ferrocifens (i.e. ferrocene-modified tamoxifens), which exhibit strong antiproliferative effects not only in hormone-dependent but also in hormone-independent breast cancer cells.

Another example of a ferrocene based drug is ferroquine [7] (FQ, SSR97193), a new antimalarial highly active against chloroquine-resistant malaria strains, and currently in phase IIb clinical trials piloted by Sanofi-Aventis. In addition, FQ has been found to display potent anticancer activity by interfering with DNA [8]. These results suggested a relation between the antitumor and the antimalarial activities of this compound [9]. Among the available strategies to design affordable and efficient drugs, the use of organometallics [10], and especially of ferrocene [5a], clearly offers new possibilities since these compounds may exhibit enhanced chemical and pharmacological properties compared to the purely organic parent drugs [6e,7b] (Chart 1).

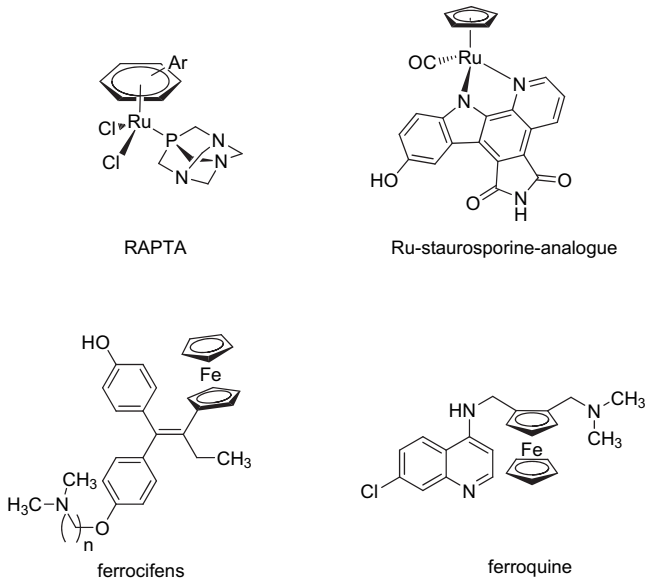


Chart 1. Chemical structures of organometallics with anticancer and antimalarial activity.

Various anticancer drugs including vinblastine, paclitaxel, colchicine, and combretastatin have been shown to modulate microtubule assembly by inhibiting tubulin polymerization or by blocking microtubule disassembly. Tubulin polymerization inhibitors characterized by the presence of an indole nucleus have been obtained from natural sources or have been prepared by semi-synthesis. Small molecules such as indole itself have been extensively studied [11]. Indeed, they are very attractive as lead compounds due to their cheap and easy synthesis. This is evidenced by the studies of the group of von Angerer [12] that has synthesized a series of 2-phenylindole derivatives and assessed their anticancer activities in human breast cancer cell lines. These compounds prevent the polymerization of the α/β-tubulin dimers to functional microtubules by binding to the colchicine-binding site and provoking cell cycle arrest in G2/M phase [12b]. The 2-phenylindole-3-carbaldehydes of this series showed pronounced cytotoxic activity. Thus the development of new 2-phenylindole derivatives as anticancer agents is of great interest. Modifications of the structure of the antimitotic 2-phenylindole-3-carbaldehydes by substitution of the 3-formyl group gave rise to methylene propanedinitrile [12c] and hydrazone [12d] derivatives that did not inhibit tubulin polymerization but were still able to block the cell cycle in G_2/M phase. QSAR [13], CoMFA, and docking studies [14] have been carried out upon 2-phenylindole derivatives to find out the structural requirements for more active antimitotic agents.

In the light of these findings, we decided to study the synthesis and characterization of new ferrocene–indole hybrids in order to compare them to their organic parent compounds. In our design, the ferrocene core was introduced into the 3 position of the 2-phenylindole scaffold (Chart 2). We studied the contribution of

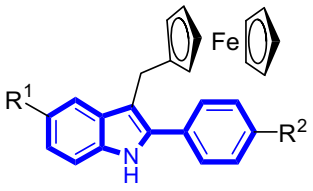


Chart 2. Compounds investigated in this study.

the ferrocene core of these new hybrid molecules in their anticancer activity against the A549 human carcinoma cell line. In addition, we tested the potential of our new derivatives against chloroquine-susceptible and chloroquine-resistant strains of *Plasmodium falciparum*.

2. Results and discussion

2.1. Chemistry

The starting 2-phenylindole derivatives (**1**–**7**) were synthesized by the classical Bischler [15] or Fischer [16] indole synthesis. The ferrocene–indole hybrids (**8**–**14**) were synthesized using a modified procedure of Boev and coworkers [17] (Scheme 1).

The 2-phenylindole derivatives were reacted with ferrocenemethanol in dichloromethane in the presence of an aqueous solution of HBF_4 at room temperature during 1 h. The two-phase system reaction is based on the generation of the corresponding α-ferrocenylcarbocation from ferrocenemethanol in strong acids and their further reaction on the nucleophilic indol 3-position. Purification of the crude products by column chromatography on silica gel using diethylether as eluent afforded the ferrocene–indole hybrids in very good yield (Scheme 1). The chemical structures of the 2-phenylindole derivatives (**1**–**7**) and the ferrocene–indole hybrids (**8**–**14**) were established unequivocally by NMR techniques using 2D homonuclear (COSY) and heteronuclear (HSQC, HMBC) experiments.

2.2. Biology

2.2.1. Cytotoxic activities

The A549 human lung carcinoma cell line was used to test the cytotoxic activity of the synthesized compounds. With the exception of **4** and **7**, all compounds exhibited cytotoxic activities with IC_{50} values below 100 μM. 5-Fluorouracil (5-FU) was used as a positive control in the cell proliferation assay, showing an IC_{50} value below 5 μM. Compounds **11**, **12** and **13** showed the highest antiproliferative effect, with IC_{50} values below 10 μM. Among these molecules, ferrocene–indole hybrid **11** showed the strongest cytotoxic activity with an IC_{50} value of 5 μM (Table 1).

For SAR analysis, some elements could be highlighted when comparing the substitution pattern of the tested compounds (**1**–**14**). The 5-position of the indole ring (R^1) is sensitive to the substitution pattern because compounds **11**, **12** and **13** had the lowest IC_{50} values. The order of potency was as follows: 5-OMe (**11**)> 5-NO_2 (**12**) > 5-Cl (**13**). The IC_{50} values of the 5-position unsubstituted compounds (R^1 = H) were higher than those of the 5-substituted compounds. Halogen substituents at the *p*-position (R^2) of the aryl ring decreased the cytotoxic properties as follows: *p*-H (**8**) > *p*-Cl (**9**) > *p*-F (**10**). The unsubstituted **8** was two-fold more active than the fluoro derivative **10**. The introduction of basic nitrogen in the isosteric exchange benzene/pyridine, ferrocene–indole hybrid **14** decreased its activity two-fold.

Table 1
Cytotoxic activities on A549 human lung carcinoma cell line of the ferrocene–indole hybrids **8**–**14** in contrast to the organic analogues **1**–**7**.

compound	Type	R^1	R^2	X	IC_{50}
1	Organic molecule	H	H	H	30 ± 7
2	Organic molecule	H	Cl	H	33 ± 8
3	Organic molecule	H	F	H	31 ± 8
4	Organic molecule	OCH_3	H	H	118 ± 4
5	Organic molecule	NO_2	H	H	14 ± 3
6	Organic molecule	Cl	H	H	15 ± 5
7	Organic molecule	H	H	N	120 ± 10
8	Organometallic molecule	H	H	H	13 ± 4
9	Organometallic molecule	H	Cl	H	15 ± 1
10	Organometallic molecule	H	F	H	26 ± 1
11	Organometallic molecule	OCH_3	H	H	5 ± 1
12	Organometallic molecule	NO_2	H	H	7 ± 1
13	Organometallic molecule	Cl	H	H	10 ± 1
14	Organometallic molecule	H	H	N	27 ± 3
5-FU	Reference				<5

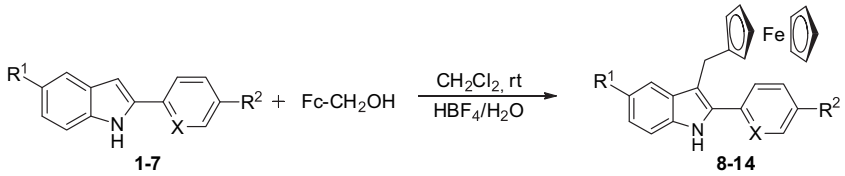
5-FU, 5-Fluorouracil.

The combination of the ferrocene core and the 2-phenylindol scaffold always increased the cytotoxicity of hybrid molecules: ferrocene–indole hybrids **8**–**14** were all more active than the corresponding purely organic compounds **1**–**7**. In this regard, ferrocene–indole hybrids **9**, **10** and **12**, with *p*-Cl, *p*-F and 5-NO_2 substituents were two-fold more active than their corresponding organic analogues **2**, **9** and **5**, respectively. The ferrocene–indole hybrids **8** and **14** were three-fold and four-fold more active than their corresponding organic analogues **1** and **7**, respectively. Finally, the ferrocene–indole hybrid **11** (with R^2 = OMe) was the most potent of the synthesized compounds (with an IC_{50} value of 5 μM) and was 25-fold more active than its corresponding precursor **4**.

2.2.2. Antimalarial activities

The *in vitro* screening assays are described in the experimental protocols section. The biological activities of the new aryl and ferrocenyl indole derivatives were compared to those of the widely used chloroquine (CQ). All the compounds were tested against a larger panel of well characterized *P. falciparum* laboratory strains or strains obtained from isolates grown in culture for an extended period of time [18] (Table 2).

Whatever the CQ susceptibility of the *P. falciparum* strains, the new derivatives only exhibited weak inhibitory effects. Moreover, no clear difference between the organic **1**–**7** and ferrocene–indole hybrids **8**–**14** could be noted. Although the interpretation of these results in terms of the structure–activity relationship (SAR) is difficult at this stage, some elements could be highlighted concerning R^1 and R^2 substituents. In the organic series, the introduction of a chlorine atom as an R^2 substituent (compound **2**) or a methoxy group as an R^1 substituent (compound **4**) caused an enhancement of the activity against *P. falciparum*. In the ferrocenic series, the most active compound was the unsubstituted indole **8**. We found no correlation between anticancer activities and antimalarial activities of these compounds. In contrast to our previous work, the most cytotoxic hybrids were not the most active on CQ-resistant strains [8].



Scheme 1. Synthesis of ferrocene-indole hybrids 8–14. Reagents and conditions: 2-arylindole (1 mmol), ferrocenemethanol (1 mmol), CH_2Cl_2, aqueous solution of HBF_4 (6 mL of 50% commercial acid + 4 mL of water), rt, 1 h.

Table 2
In vitro antiplasmodial activity of 2-phenylindoles and 3-ferrocenylmethyl-2-phenylindoles.

	IC_{50} in μM[a]							
Strains	3D7	D6	FCM29	IMT 10500	K14	K4	PA	W2
Origin	Africa	Sierra Leone	Cameroon	Comoros	Cambodia	Cambodia	Uganda	Indochina
1	>100	44.0	35.3	44.6	28.7	90.1	31.5	35.8
2	26.4	30.2	43.2	32.8	25.1	18.2	15.1	26.5
3	18.6	25.4	100	28.5	>100	52.2	>100	26.2
4	23.0	24.7	28.2	21.2	27.3	25.1	37.3	17.6
5	22.8	22.3	21.0	30.5	24.9	22.2	31.5	24.0
6	34.0	29.5	33.0	32.4	26.9	27.1	12.3	19.7
7	>100	29.2	25.6	43.3	30.9	39.4	>100	30.8
8	28.2	22.7	25.4	25.8	22.3	18.8	24.6	26.7
9	30.6	33.3	25.2	36.4	37.7	38.4	31.0	33.2
10	38.2	43.6	31.9	29.7	40.8	14.8	17.6	29.3
11	38.6	29.0	44.0	26.4	36.4	32.1	31.0	29.6
12	31.5	28.0	26.0	25.7	25.3	19.4	25.1	28.6
13	31.9	13.3	25.8	30.3	25.2	14.2	20.4	30.0
14	28.3	26.0	30.8	41.0	27.5	22.3	16.9	28.2
IC_{50} in nM								
CQ	25	25	502	51	662	491	287	539
FQ	3.5	5.2	6.8	4.6	13.0	7.5	6.4	6.6

[a] IC_{50} are geometric means of 3–4 experiments.

3. Conclusion

In summary, we report a convenient one-step, high yield synthetic procedure for the preparation of the 3-ferrocenyl-2-phenylindole derivatives, **8**–**14**. The design of these compounds constitutes the first bioorganometallic approach for modifying the 2-phenylindole framework present in several potent antimitotic drugs. These new ferrocene–indole hybrids and their organic analogues were tested for their cytotoxic and antiplasmodial activities. These compounds showed only moderate antimalarial activity and the presence or absence of the ferrocenyl moiety only slightly affected this. Ferrocene–indole hybrids **11**, **12**, and **13** were the most potently cytotoxic compounds with IC_{50} values below 10 μM. The ferrocene–indole hybrids **8**–**14** were found to be markedly more cytotoxic than the organic series (compounds **1**–**7**). Notably we observed a 25-fold increase in potency for the ferrocenic 5-OMe derivative **11**, with an IC_{50} value of 5 μM. Future work will be aimed at the evaluation of the mode of action of the synthesized hybrids molecules and the preparation of new analogues bearing alkyl groups at R^1 and alkoxy substituents at R^2, taking into account QSAR and CoMFA analysis carried out previously on 3-carbaldehyde-2-phenylindole derivatives.

4. Experimental

4.1. Chemistry

Materials and methods. Reagents were obtained from commercial sources and used as received. All reactions were carried out with dry, freshly distilled solvents. Column chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–240 mesh). Analytical TLC was performed on SiO_2 (Merck silica gel 60 F_{254}) plates. Melting points were determined on a Gallenkamp apparatus and are not corrected. Elemental analyses were carried out at the Serveis Cientifico-Tècnics (*Universitat Barcelona*). Mass spectra (ESI^+) were performed at the Servei d'Espectrometria de Masses (*Universitat de Barcelona*). Infrared spectra were obtained with a Nicolet 400FTIR instrument using KBr pellets. Only noteworthy IR absorptions are listed (cm^{-1}). Chemical shifts of ^1H NMR spectra are reported in ppm downfield (δ) from Me_4Si. For ^{13}C NMR spectra chemical shifts are reported relative to the δ 77.00 resonance of $CDCl_3$. Unless otherwise noted ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 400 and 100 MHz, respectively and registered with a Mercury-400 MHz. Coupling constants (J) are reported in Hz. All NMR assignments were made on the basis of two-dimensional NMR experiments (gCOSY gHSQC and gHMBC). ^{19}F NMR spectra of **2** and **10** were recorded with a Mercury 400 instrument and the reference was TFA [δ (^{19}F) = −78.5 ppm].

4.1.1. Full description of ^1H, ^{19}F and ^{13}C NMR spectra for 2-pheylylindoles (**1**–**7**) [19]

The full description of ^1H, ^{19}F and ^{13}C NMR spectra for 2-phenylylindoles (**1**–**7**) is given, as these data, to the best of our knowledge, were found to be incomplete in the literature [15,16].

*4.1.1.1. 2-Phenyl-1H-indole (**1**).* ^1H NMR (gCOSY) 8.31 (b s, 1H, NH-indol), 7.64 (d, J = 8 Hz, 2H, H-2′ and H-6′), 7.63 (d, J = 8 Hz, 1H, H-4), 7.43 (m, 2H, H-3′ and H-5′), 7.39 (d, J = 8 Hz, 1H, H-7), 7.32 (tt, J = 7.6 and 1.2 Hz, 1H, H-4′), 7.19 (td, J = 8 and 1.1 Hz, 1H, H-6), 7.14 (td, J = 8 and 1.1 Hz, 1H, H-5), 6.82 (s, 1H, H-3). ^{13}C NMR (gHSQC, gHMBC) 137.8 (C-1′), 136.8 (C-7a), 132.3 (C-2), 129.2 (C-3a), 129.0 (C-2′ and C-6′), 127.7 (C-4′), 125.1 (C-3′ and C-5′), 122.3 (C-6), 120.6 (C-4), 120.3 (C-5), 110.9 (C-7), 99.9 (C-3).

*4.1.1.2. 2-(4-Chlorophenyl)-1H-indole (**2**).* ^1H NMR (gCOSY) 8.23 (b s, 1H, NH-indol), 7.62 (d, J = 7.8 Hz, 1H, H-4), 7.56 (m, 2H, H-2′ and H-6′), 7.40 (m, 2H, H-3′ and H-5′), 7.38 (dd, J = 8 and 0.9 Hz, 1H, H-7), 7.20 (ddd, J = 8.0, 7.1 and 1.1 Hz, 1H, H-6), 7.13 (ddd, J = 7.7, 7.0 and 1.1 Hz, 1H, H-5), 6.80 (dd, J = 2.1 and 0.9 Hz, 1H, H-3). ^{13}C NMR (gHSQC, gHMBC) 136.9 (C-7a), 136.6 (C-2), 133.4 (C-4′), 130.8 (C-1′), 129.2 (C-3′ and C-5′), 129.1 (C-3a), 126.3 (C-2′ and C-6′), 122.7 (C-6), 120.7 (C-4), 120.4 (C-5), 110.9 (C-7), 100.4 (C-3).

*4.1.1.3. 2-(4-Fluorophenyl)-1H-indole (**3**).* ^1H NMR (gCOSY) 8.25 (b s, 1H, NH-indol), 7.58–7.65 (m, 3 H, H-4, H-2′ and H-6′), 7.39 (dd, J = 8 and 1 Hz, 1H, H-7), 7.20 (td, J = 8 and 1.2 Hz, 1H, H-6), 7.10–7.18 (m, 3 H, H-5, H-3′ and H-5′), 6.76 (d, J = 3 Hz, 1H, H-3). ^{13}C NMR (gHSQC, gHMBC) 163.6, 161.2 (C-4′), 137.0 (C-7a), 136.8 (C-2), 129.2 (C-3a), 128.8 (C-1′), 126.9, 126.8 (C-2′ and C-6′), 122.4 (C-6), 120.6 (C-4), 120.4 (C-5), 116.2, 115.9 (C-3′ and C-5′), 110.9 (C-7), 99.9 (C-3). ^{19}F NMR -114.37.

*4.1.1.4. 5-Methoxy-2-phenyl-1H-indole (**4**).* ^1H NMR (gCOSY) 8.20 (b s, 1H, NH-indol), 7.64 (m, 2H, H-2′ and H-6′), 7.43 (t, J = 7.6 Hz, 2H, H-3′ and H-5′), 7.31 (m, 1H, H-4′), 7.29 (d, J = 8.8 Hz, 1H, H-7), 7.09

(d, $J = 2$ Hz, 1H, H-4), 6.86 (dd, $J = 8.8$ and 2.4 Hz, 1H, H-6), 6.76 (d, $J = 2$ Hz, 1H, H-3), 3.87 (s, 3 H, OCH_3). ^{13}C NMR (gHSQC, gHMBC) 154.5, (C-5), 138.6 (C-2), 132.5 (C-1′), 132.0 (C-7a), 129.7 (C-3a), 129.0 (C-3′ and C-5′), 127.6 (C-4′), 125.0 (C-2′ and C-6′), 112.6 (C-6), 111.6 (C-7), 102.3 (C-4), 99.8 (C-3), 55.8 (CH_3).

*4.1.1.5. 5-Nitro-2-phenyl-1H-indole (**5**).* ^1H NMR (gCOSY) 8.78 (b s, 1H, NH-indol), 8.59(d, $J = 2$ Hz, 1H, H-4), 8.12 (dd, $J = 9.2$ and 2 Hz, 1H, H-6), 7.70 (m, 2H, H-2′ and H-6′), 7.50 (td, $J = 7.6$ and 1.4 Hz, 2H, H-3′ and H-5′), 7.44 (d, $J = 9.2$ Hz, 1H, H-7), 7.41 (tt, $J = 7.4$ and 1.6 Hz, 1H, H-4′), 6.98 (s, 1H, H-3). ^{13}C NMR (gHSQC, gHMBC) 142.3, (C-3a), 141.2 (C-2), 139.7 (C-7a), 131.1 (C-1′), 129.3 (C-3′ and C-5′), 128.8 (C-4′), 128.6 (C-5), 125.4 (C-2′ and C-6′), 118.0 (C-6), 117.7 (C-4), 110.9 (C-7), 101.6 (C-3).

*4.1.1.6. 5-Chloro-2-phenyl-1H-indole (**6**).* ^1H NMR (gCOSY) 8.37 (b s, 1H, NH-indol), 7.64 (dt, $J = 7.2$ and 1.2 Hz, 2H, H-2′ and H-6′), 7.58 (d, $J = 2$ Hz, 1H, H-4), 7.44 (td, $J = 7.4$ and 1.4 Hz, 2H, H-3′ and H-5′), 7.34 (tt, $J = 7.4$ and 1.2 Hz, 1H, H-4′), 7.29 (d, $J = 8.8$ Hz, 1H, H-7), 7.13 (dd, $J = 9$ and 2 Hz, 1H, H-6), 6.75 (s, 1H, H-3). ^{13}C NMR (gHSQC, gHMBC) 139.3 (C-2), 135.1 (C-7a), 131.8 (C-1′), 130.3 (C-3a), 129.1 (C-3′ and C-5′), 128.1 (C-4′), 125.8 (C-5), 125.2 (C-2′ and C-6′), 122.5 (C-6), 120.0 (C-4), 111.9 (C-7), 99.5 (C-3).

*4.1.1.7. 2-(2pyiridyl)-1H-indole (**7**).* ^1H NMR (gCOSY) 9.86 (b s, 1H, NH-indol), 8.57 (dm, $J = 4.8$ Hz, 1H, H-3′), 7.80 (m, 1H, H-6′), 7.70 (td, $J = 7.6$ and 1.6 Hz, 1H, H-5′), 7.65 (d, $J = 7.6$ Hz, 1H, H-4), 7.37 (dm, $J = 8$ Hz, 1H, H-7), 7.21 (ddd, $J = 8.2$, 7 and 1.2 Hz, 1H, H-6), 7.16 (ddd, $J = 7.4$, 4.8 and 1 Hz, 1H, H-4′), 7.11 (ddd,, $J = 7.8$, 7.1 and 0.9 Hz, 1H, H-5), 7.02 (m, 1H, H-3). ^{13}C NMR (gHSQC, gHMBC) 150.4 (C-1′), 149.1 (C-3′), 136.7 (C-2), 136.62 (C-5′), 136.59 (C-7a), 129.1 (C-3a), 123.1 (C-6), 122.0 (C-4′), 121.1 (C-4), 120.1 (C-5), 119.9 (C-6′), 111.4 (C-7), 100.6 (C-3).

*4.1.2. General synthetic procedure for the preparation of 3-ferrocenylmethyl-2-pheylindoles (**8**–**14**)*

A slightly modified procedure of Boev and coworkers [17] was followed for the synthesis of the 3-ferrocenylmethyl-2-phenylindoles. To a stirred solution of the parent 2-phenylindole derivative (**1**–**7**, 1 mmoL) and ferrocenemethanol (216 mg, 1 mmoL) in dichloromethane (25 mL), 10 mL of an aqueous solution of HBF_4 (6 mL of 50% commercial acid + 4 mL H_2O) was added dropwise. After vigorous stirring for 1 h, the mixture was quenched with water (40 mL). The phases were separated, and the aqueous phase extracted with dichloromethane (2 × 20 mL) [20]. The combined organic extracts were washed with water (2 × 10 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography on a short pad of silica gel using diethylether as eluent. The ether was evaporated under reduced pressure to yield the desired 3-ferrocenylmethyl derivatives (**8**–**14**) in very high yield.

*4.1.2.1. 3-Ferrocenylmethyl-2-phenyl-1H-indole (**8**).* Yellow solid, mp 128–130 °C. Yield 92%. Anal. Calc. For $C_{25}H_{21}FeN$: C, 76.92; H, 5.37; N, 3.58. Found: C, 76.59; H, 5.31; N, 3.78%. MS (ESI^+): $m/z = 391.11$ [M^+]. IR: 3500, 3403, 3383, 1456, 765, 746, 699, 501, 484. ^1H NMR (gCOSY) 8.00 (b s, 1H, NH-indol), 7.60–7.70 (m, 3 H, H-6, H-2′ and H-6′), 7.51 (t, $J = 7.6$ Hz, 1H, H-3′ and H-5′), 7.41 (d, $J = 7.6$ Hz, 1H, H-7), 7.36 (m, 1H, H-4), 7.18 (td, $J = 7.4$ and 1.2 Hz, 1H, H-5), 7.12 (m, 1H, H-4′), 4.13 (s, 2H, H^2 and H^5, C_5H_4), 4.02 (s, 7 H, H^3, H^4, C_5H_4 and C_5H_5), 3.99 (s, 2H, CH_2). ^{13}C NMR (gHSQC, gHMBC) 136.0 (C-7a), 134.3 (C-3a), 133.5 (C-1′), 128.8 (C-2′ and C-6′), 128.2 (C-3′ and C-5′), 127.7 (C-4′), 125.0 (C-2), 122.2 (C-6), 119.60 (C-4), 119.57 (C-5), 113.0 (C-3), 110.7 (C-7), 89.0 (C^1), 68.8 (C^2, C^5), 68.6 (C_5H_5), 66.9 (C^3, C^4), 24.6 (CH_2).

*4.1.2.2. 2-(4-Chlorophenyl)-3-ferrocenylmethyl-1H-indole (**9**).* Dark yellow solid, mp 179–181 °C. Yield 92%. Anal. Calc. For $C_{25}H_{20}ClFeN$: C, 70.52; H, 4.70; N, 3.29. Found: C, 70.16; H, 4.73; N, 3.30%. MS (ESI^+): $m/z = 425$ [M^+]. IR: 3540, 3413, 3397, 1483, 1455, 1435, 1335, 1311, 1105, 1089, 1010, 997, 832, 738, 495. ^1H NMR (gCOSY) 7.94 (b s, 1H, NH-indol), 7.63 (d, $J = 8$ Hz, 1H, H-4), 7.53 (d, $J = 8$ Hz, 2H, H-2′ and H-6′), 7.46 (d, $J = 8$ Hz, 2H, H-3′ and H-5′), 7.33 (d, $J = 7.6$ Hz, 1H, H-7), 7.19 (t, $J = 7.4$ Hz, 1H, H-6), 7.12 (dd, $J = 7.4$ and 8 Hz, 1H, H-5), 4.06 (s, 5 H, C_5H_5), 4.12 (s, 2H, H^2 and H^5, C_5H_4), 4.00 (s, 2H, H^3 and H^4, C_5H_4), 3.94 (s, 2H, CH_2). ^{13}C NMR (gHSQC, gHMBC) 135.9 (C-7a), 133.6 (C-4′), 133.0 (C-2), 131.7 (C-1′), 129.4 (C-2′ and C-6′), 129.0 (C-3′ and C-5′), 128.9 (C-3a), 122.5 (C-6), 119.8 (C-4), 119.6 (C-5), 113.6 (C-3), 110.8 (C-7), 88.9 (C^1), 68.8 (C^2 and C^5), 68.7 (C_5H_5), 67.0 (C^3 and C^4), 24.6 (CH_2).

*4.1.2.3. 3-Ferrocenylmethyl-2-(4-fluorophenyl)-1H-indole (**10**).* Yellow solid, mp 146–148 °C. Yield 94%. Anal. Calc. For $C_{25}H_{20}FFeN$: C, 73.37; H, 4.89; N, 3.42. Found: C, 73.28; H, 4.99; N, 3.50%. MS (ESI^+): $m/z = 409$ [M]+H.$^+$ IR: 3418, 1502, 1457, 1436, 1227, 1216, 1156, 1101, 841, 815, 735, 489. ^1H NMR (gCOSY) 7.94 (b s, 1H, NH-indol), 7.62 (d, $J = 8$ Hz, 1H, H-4), 7.54–7.60 (m, 2H, H-2′ and H-6′), 7.35 (d, $J = 8$ Hz, 1H, H-7), 7.15–7.22 (m, 3 H, H-6, H-3′ and H-5′), 7.12 (m, 1H, H-5), 4.12 (s, 2H, H^2 and H^5, C_5H_4), 4.04 (s, 5 H, C_5H_5), 4.00 (s, 2H, H^3 and H^4, C_5H_4), 3.93 (s, 2H, CH_2). ^{13}C NMR (gHSQC, gHMBC) 163.6, 161.2 (C-4′), 135.8 (C-7a), 133.3 (C-2), 130.0, 129.9 (C-2′ and C-6′), 129.4 (C-1′), 129.1 (C-3a), 122.3 (C-6), 119.7 (C-5), 119.6 (C-4), 115.9, 115.8 (C-3′ and C-5′), 113.1 (C-3), 110.7 (C-7), 88.9 (C^1), 68.8 (C^2 and C^5), 68.7 (C_5H_5), 67.1 (C^3 and C^4), 24.6 (CH_2). ^{19}F NMR -114.37.

*4.1.2.4. 3-Ferrocenylmethyl-5-methoxy-2-phenyl-1H-indole (**11**).* Grey solid, mp 141–143 °C. Yield 90%. Anal. Calc. For $C_{26}H_{22}FeNO$: C, 74.12; H, 5.50; N, 3.32. Found: C, 73.78; H, 5.67; N, 3.31%. MS (ESI^+): $m/z = 421$ [M]+H$^+$. IR: 3386, 1481, 1449, 1214, 1021, 828, 770, 698, 510, 496. ^1H NMR (gCOSY) 7.87 (b s, 1H, NH-indol), 7.60 (dd, $J = 7.8$ and 1.2 Hz, 2H, H-2′ and H-6′), 7.49 (t, $J = 7.8$ Hz, 2H, H-3′ and H-5′), 7.38 (tt, $J = 7.6$ and 1.2 Hz, 1H, H-4′), 7.24 (d, $J = 8.8$ Hz, 1H, H-7), 7.04 (d, $J = 2.6$ Hz, 1H, H-4), 6.84 (dd, $J = 8.6$ and 2.6 Hz, 1H, H-6), 4.16 (s, 2H, H^2 and H^5, C_5H_4), 4.05 (s, 5 H, C_5H_5), 4.02 (s, 2H, H^3 and H^4, C_5H_4), 3.94 (s, 2H, CH_2), 3.85 (s, 3 H, OCH_3). ^{13}C NMR (gHSQC, gHMBC) 154.2 (C-5), 135.2 (C-2), 133.3 (C-1′), 131.0 (C-7a) 129.6 (C-3a), 128.8 (C-3′ and C-5′), 128.1 (C-2′ and C-6′), 127.7 (C-4′), 112.7 (C-3), 112.2 (C-6), 111.4 (C-7), 101.7 (C-4), 90.0 (C^1), 69.4 (C^2, C^5 and C_5H_5), 67.7 (C^3 and C^4), 55.9 (OCH_3), 24.6 (CH_2).

*4.1.2.5. 3-Ferrocenylmethyl-5-nitro-2-phenyl-1H-indole (**12**).* Yellow-orange solid, mp 185 °C. Yield 93%. Anal. Calc. For $C_{25}H_{20}FeN_2O_2$: C, 68.82; H, 4.62; N, 6.42. Found: C, 68.94; H, 4.61; N, 6.37%. MS (ESI^+): $m/z = 436.4$ [M^+]. IR: 3470, 3450, 3382, 3325, 1515, 1473, 1328, 1300, 815, 737, 699, 480. ^1H NMR (gCOSY) 8.60 (d, $J = 2$ Hz, 1H, H-4), 8.34 (b s, 1H, NH-indol), 8.10 (dd, $J = 8.6$ and 2.2 Hz, 1H, H-6), 7.63 (m, 2H, H-2′ and H-6′), 7.55 (t, $J = 7.6$ Hz, 2H, H-3′ and H-5′), 7.47 (t, $J = 7.4$ Hz, 1H, H-4′), 7.37 (d, $J = 8.8$ Hz, 1H, H-7), 4.11 (t, $J = 1.6$ Hz, 2H, H^2 and H^5, C_5H_4), 4.07 (s, 5 H, C_5H_5), 4.03 (t, $J = 1.8$ Hz, 2H, H^3 and H^4, C_5H_4), 4.01 (s, 2H, CH_2). ^{13}C NMR (gHSQC, gHMBC) 141.7 (C-3a), 138.7 (C-7a), 133.3 (C-1′), 137.3 (C-2) 131.9 (C-1′), 129.1 (C-3′ and C-5′), 128.7 (C-5), 128.6 (C-4′), 128.3 (C-2′ and C-6′), 117.9 (C-6), 116.8 (C-4), 115.2 (C-3), 110.7 (C-7), 88.1 (C^1), 68.81 (C^2 and C^5), 68.80 (C_5H_5), 67.4 (C^3 and C^4), 24.5 (CH_2).

*4.1.2.6. 5-Chloro-3-ferrocenylmethyl-2-phenyl-1H-indole (**13**).* Orange solid, mp 140–143 °C. Yield 96%. Anal. Calc. For $C_{25}H_{20}FeClN$: C, 70.53; H, 4.74; N, 3.29. Found: C, 70.42; H, 4.97; N, 3.45%. MS (ESI^+): $m/z = 425.07$ [M^+]. IR: 3500, 3407, 1638, 1580, 1463, 1450, 1425, 1307, 1104, 1000, 815, 797, 763, 699, 484. ^1H NMR (gCOSY) 8.01 (b s,

1H, NH-indol), 7.62 (d, J = 7. 2 Hz, 2H, H-2′ and H-6′), 7.57 (d, J = 2 Hz, 1H, H-4), 7.51 (t, J = 7.2 Hz, 2H, H-3′ and H-5′), 7.42 (t, J = 7.2 Hz, 1H, H-4′), 7.26 (d, J = 8.4 Hz, 1H, H-7), 7.13 (dd, J = 8.6 and 2.2, 1H, H-6), 4.10 (t, J = 1.8 Hz, 2H, H^2 and H^5, C_5H_4), 4.03 (s, 5 H, C_5H_5), 4.00 (t, J = 2 Hz, 2H, H^3 and H^4, C_5H_4), 3.94 (s, 2H, CH_2). ^{13}C NMR (gHSQC, gHMBC) 135.7 (C-2), 134.1 (C-7a), 132.8 (C-1′), 130.3 (C-5), 128.9 (C-3′ and C-5′), 128.2 (C-2′ and C-6′), 128.1 (C-4′), 125.2 (C-3a), 122.4 (C-6), 119.0 (C-4), 112.7 (C-3), 111.7 (C-7), 88.6 (C^1), 68.7 (C^2 and C^5), 68.6 (C_5H_5), 67.1 (C^3 and C^4), 24.5 (CH_2).

*4.1.2.7. 3-Ferrocenylmethyl-2-(2pyridyl)-1H-indole (**14**).* Yellow solid, mp 133–136 °C. Yield 83%. Anal. Calc. For $C_{24}H_{20}FeN_2$: C, 73.48; H, 5.14; N, 7.14. Found: C, 73.10; H, 5.04; N, 6.83%. MS (ESI^+): m/z = 393.11{[M]+H}$^+$. IR: 3500, 3404, 3200, 3087, 2921, 1764, 1590, 1563, 1451, 1337, 1320, 1104, 999, 818, 742, 483. ^1H NMR (gCOSY) 9.55 (b s, 1H, NH-indol), 8.62 (dd, J = 3.2, 1.2 Hz, 1H, H-3′), 7.80 (d, J = 8 Hz, 1H, H-6′), 6.69–7.74 (m, 2H, H-4 and H-5′), 7.38 (d, J = 8 Hz, 1H, H-7), 7.23 (td, J = 7.6 and 1.6 Hz, 1H, H-6), 7.10–7.18 (m, 2H, H-5 and H-4′), 7.31 (td, J = 6.8 and 1.2 Hz, 1H, H-5), 4.18 (m, 4 H, CH_2, H^2 and H^5, C_5H_4), 4.09 (s, 5 H, C_5H_5), 4.01 (t, J = 2.4 Hz, 2H, H^3 and H^4, C_5H_4). ^{13}C NMR (gHSQ, gHMBC) 150.7 (C-1′), 149.3 (C-3′), 136.5 (C-5′), 135.4 (C-7a), 132.1 (C-2), 129.7 (C-3a), 123.3 (C-6), 121.6 (C-4′), 121.2 (C-6′), 119.7 (C-4), 119.4 (C-5), 114.4 (C-3), 111.2 (C-7), 88.5 (C^1), 68.7 (C_5H_5), 68.6 (C^2 and C^5), 67.1 (C^3 and C^4), 25.0 (CH_2).

4.2. Biology

4.2.1. Cell culture

Human lung carcinoma A549 cells (obtained from the American Type Culture Collection) were used in all the experiments. A549 cells were grown as a monolayer culture in minimum essential medium (DMEM with L-glutamine, without glucose and without sodium pyruvate) in the presence of 10% heat-inactivated fetal calf serum, 10 mM of D-glucose and 0.1% streptomycin/penicillin in standard culture conditions.

4.2.2. Cell proliferation assay

The assay was performed by a variation of the method described by Mosmann et al. [21] as specified by Matito and coworkers [22]. Briefly, 3×10^3 A549 cells/well were cultured in 96 well plates. Concentrations that inhibited cell growth by 50% (IC_{50}) after 72 h of treatment were calculated based on the survival rate compared with untreated cells. Relative cell viability was measured by the absorbance on an ELISA plate reader (Tecan Sunrise MR20-301, TECAN, Salzburg, Austria) at 550 nm.

4.2.3. Antiplasmodial assay

Eight parasite strains or isolates from a wide panel of countries (Africa (3D7), Cambodia (K2 and K14), Cameroon (FCM29), Comoros (IMT10500), Indochina (W2), Sierra Leone (D6), and Uganda (PA)) were maintained in culture in RPMI 1640 (Invitrogen, Paisley, United Kingdom), supplemented with 10% human serum (Abcys S.A. Paris, France) and buffered with 25 mM HEPES and 25 mM $NaHCO_3$. Parasites were grown in A-positive human blood under controlled atmospheric conditions that consisted of 10% O_2, 5% CO_2 and 85% N_2 at 37 °C with a humidity of 95%.

Chloroquine diphosphate (CQ) was purchased from Sigma (Saint Louis, MO). FQ base was obtained from Sanofi-Aventis (France). CQ was resuspended in water in concentrations ranging between 5 and 3200 nM. FQ and synthetic compounds were resuspended in DMSO and then diluted in RPMI-DMSO (99v/1v) to obtain final concentrations ranging from 0.125 to 500 nM and 0.1 μM–100 μM, respectively.

For *in vitro* isotopic microtests, 25 μL/well of antimalarial drug and 200 μL/well of the parasitized red blood cell suspension (final parasitemia, 0.5%; final hematocrit, 1.5%) were distributed into 96 well plates. Parasite growth was assessed by adding 1 μCi of tritiated hypoxanthine with a specific activity of 14.1 Ci/mmol (Perkin–Elmer, Courtaboeuf, France) to each well at time zero. The plates were then incubated for 48 h in controlled atmospheric conditions. Immediately after incubation, the plates were frozen and thawed to lyse erythrocytes. The contents of each well were collected on standard filter microplates (Unifilter GF/B; Perkin–Elmer) and washed using a cell harvester (Filter-Mate Cell Harvester; Perkin–Elmer). Filter microplates were dried, and 25 μL of scintillation cocktail (Microscint O; Perkin–Elmer) was placed in each well. Radioactivity incorporated by the parasites was measured with a scintillation counter (Top Count; Perkin–Elmer).

The IC_{50}, the drug concentration able to inhibit 50% of parasite growth, was assessed by identifying the drug concentration corresponding to 50% of the uptake of tritiated hypoxanthine by the parasite in the drug-free control wells. The IC_{50} value was determined by non-linear regression analysis of log-based dose-response curves (Riasmart™, Packard, Meriden, USA). IC_{50} are expressed as geometric means of 3–4 experiments.

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References

[1] R.D. Adams, J. Organomet. Chem. 694 (2009) 801–802.
[2] (a) A. Dorcier, P.J. Dyson, C. Gossens, U. Rothlisberger, R. Scopelliti, I. Tavernelli, Organometallics 24 (2005) 2114–2123;
(b) P.J. Dyson, G. Sava, Dalton Trans. 16 (2006) 1929–1933;
(c) B. Dutta, C. Scolaro, R. Scopelliti, P.J. Dyson, K. Severin, Organometallics 27 (2008) 1355–1357;
(d) A.K. Renfrew, A.D. Phillips, A.E. Egger, C.G. Hartinger, S.S. Bosquain, A.A. Nazarov, B.K. Keppler, L. Gonsalvi, M. Peruzzini, P.J. Dyson, Organometallics 28 (2009) 1165–1172.
[3] (a) D.S. Williams, G.E. Atilla, H. Bregman, A. Arzoumanian, P.S. Klein, E. Meggers, Angew. Chem. Int. Ed. 44 (2005) 1984–1987;
(b) H. Bregman, E. Meggers, Org. Lett. 8 (2006) 5465–5468;
(c) E. Meggers, Curr. Opin. Chem. Biol. 11 (2007) 287–292;
(d) E. Meggers, G.E. Atilla-Gokcumen, H. Bregman, J. Maksimoska, S.P. Mulcahy, N. Pagano, D.S. Williams, Synlett (2007) 1177–1189. doi:10.1055/s-2007-973893;
(e) K.S.M. Smalley, R. Contractor, N.K. Haass, A.N. Kulp, G.E. Atilla-Gokcumen, D.S. Williams, H. Bregman, K.T. Flaherty, M.S. Soengas, E. Meggers, M. Herlyn, Cancer Res. 67 (2007) 209–217.
[4] (a) H. Tamura, M. Miwa, Chem. Lett. (1997) 1177–1178;
(b) D. Osella, M. Ferrali, P. Zanello, F. Laschi, M. Fontani, C. Nervi, G. Cavigiolio, Inorg. Chim. Acta 306 (2000) 42–48;
(c) G. Tabbì, C. Cassino, G. Cavigiolio, D. Colangelo, A. Ghiglia, I. Viano, D. Osella, J. Med. Chem. 45 (2002) 5786–5796.
[5] (a) M.F.R. Fouda, M.M. Abd-Elzaher, R.A. Abdelsamaia, A.A. Labib, Appl. Organomet. Chem. 21 (2007) 613–625;
(b) D.R. van Staveren, N. Metzler-Nolte, Chem. Rev. 104 (2004) 5931–5985.
[6] (a) S. Top, A. Vessières, G. Leclercq, J. Quivy, J. Tang, J. Vaissermann, M. Huché, G. Jaouen, Chem. . A Eur. J. 9 (2003) 5223–5236;
(b) G. Jaouen, S. Top, A. Vessières, G. Leclercq, M.J. McGlinchey, Curr. Med. Chem. 11 (2004) 2505–2517;
(c) A. Vessières, S. Top, P. Pigeon, E. Hillard, L. Boubeker, D. Spera, G. Jaouen, J. Med. Chem. 48 (2005) 3937–3940;
(d) E. Hillard, A. Vessières, L. Thouin, G. Jaouen, C. Amatore, Angew. Chem. Int. Ed. 45 (2006) 285–290;
(e) A. Vessieres, S. Top, W. Beck, E. Hillard, G. Jaouen, Dalton Trans. 4 (2006) 529–541;
(f) A. Nguyen, E.A. Hillard, A. Vessières, S. Top, P. Pigeon, G. Jaouen, Chimia 61 (2007) 716–724;
(g) O. Buriez, J.M. Heldt, E. Labbé, A. Vessières, G. Jaouen, C. Amatore, Chem. A Eur. J. 14 (2008) 8195–8203;
(h) Q. Michard, G. Jaouen, A. Vessieres, B.A. Bernard, J. Inorg. Biochem. 102 (2008) 1980–1985;
(i) P. Pigeon, S. Top, O. Zekri, E.A. Hillard, A. Vessières, M.-A. Plamont, O. Buriez,

E. Labbé, M. Huché, S. Boutamine, C. Amatore, G. Jaouen, J. Organomet. Chem. 694 (2009) 895–901;
(j) M. Gormen, D. Plazuk, P. Pigeon, E.A. Hillard, M.-A. Plamont, S. Top, A. Vessières, G. Jaouen, Tetrahedron Lett. 51 (2010) 118–120.

[7] (a) F. Dubar, J. Khalife, J. Brocard, D. Dive, C. Biot, Molecules 13 (2008) 2900–2907;
(b) D. Dive, C. Biot, ChemMedChem 3 (2008) 383–391.

[8] N.I. Wenzel, N. Chavain, Y. Wang, W. Friebolin, L. Maes, B. Pradines, M. Lanzer, V. Yardley, R. Brun, C. Herold-Mende, C. Biot, K. Tóth, E. Davioud-Charvet, J. Med. Chem. 53 (2010) 3214–3226.

[9] (a) A. Nzila, J. Okombo, R.P. Becker, R. Chilengi, T. Lang, T. Niehues, Trends Parasitol. 26 (2010) 125–129;
(b) S. Kozlov, N.C. Waters, M. Chavchich, Infect. Disord. . Drug Targets 10 (2010) 165–190;
(c) P. Lawton, M. Sarciron, A. Pétavy, Drugs of the Future 31 (2006) 793–809;
(d) M. Klinkert, V. Heussler, Mini-Reviews Med. Chem. 6 (2006) 131–143;
(e) B. Kappes, P. Rohrbach, Future Microbiol. 2 (2007) 409–423;
(f) N. Kongkathip, N. Pradidphol, K. Hasitapan, R. Grigg, W.- Kao, C. Hunte, N. Fisher, A.J. Warman, G.A. Biagini, P. Kongsaeree, P. Chuawong, B. Kongkathip, J. Med. Chem. 53 (2010) 1211–1221.

[10] (a) C.S. Allardyce, A. Dorcier, C. Scolaro, P.J. Dyson, Appl. Organomet. Chem. 19 (2005) 1–10;
(b) C.G. Hartinger, P.J. Dyson, Chem. Soc. Rev. 38 (2009) 391–401;
(c) N. Chavain, C. Biot, Curr. Med. Chem. 17 (2010) 2729–2745.

[11] For a review see: A. Brancale, R. Silvestri Med. Res. Rev. 27 (2007) 209–238 and references cited herein.

[12] (a) R. Gastpar, M. Goldbrunner, D. Marko, E. von Angerer, J. Med. Chem. 41 (1998) 4965–4972;
(b) D. Kaufmann, M. Pojarová, S. Vogel, R. Liebl, R. Gastpar, D. Gross, T. Nishino, T. Pfaller, E. von Angerer, Bioorg. Med. Chem. 15 (2007) 5122–5136;
(c) M. Pojarová, D. Kaufmann, R. Gastpar, T. Nishino, P. Reszka, P.J. Bednarski, E. von Angerer, Bioorg. Med. Chem. 15 (2007) 7368–7379;
(d) S. Vogel, D. Kaufmann, M. Pojarová, C. Müller, T. Pfaller, S. Kühne, P.J. Bednarski, E. von Angerer, Bioorg. Med. Chem. 16 (2008) 6436–6447.

[13] A.K. Halder, N. Adhikari, T. Jha, Bioorg. Med. Chem. Lett. 19 (2009) 1737–1739.

[14] S.Y. Liao, L. Qian, T.F. Miao, H.L. Lu, K.C. Zheng, Eur. J. Med. Chem. 44 (2009) 2822–2827.

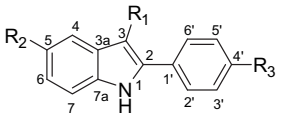
[15] Bischler indol synthesis (only selected articles): (a) V. Sridharan, S. Perumal, C. Avendaño, J.C. Menéndez, Synlett (2006) 91–95;
(b) J. Schmitt, C. Perrin, M. Langlois, M. Suquet, Bull. Soc. Chim. Fr. (1969) 1227–1236;
(c) R. Gastpar, M. Goldbrunner, D. Marko, E. von Angerer, J. Med. Chem. 41 (1998) 4965–4972;
(d) E. von Angerer, J. Prekajac, J. Strohmeier, J. Med. Chem. 27 (1984) 1439–1447;
(e) E. von Angerer, J.J. Strohmeier, Med. Chem. 30 (1987) 131–136.

[16] Fischer indol synthesis: (only selected articles): (a) W.E. Noland, K.R. Rush, L.R. Smith, J. Org. Chem. 31 (1966) 65–69 (see this article for 5-nitro-2-phenylindole, 5);
(b) R.P. Thummel, V. Hedge, J. Org. Chem. 54 (1989) 1720–1725 (see this article for the 2-pyridyl derivatives);
(c) Q. Liu, M.S. Mudadu, H. Schmider, R. Thummel, Y. Tao, S. Wang, Organometallics 21 (2002) 4743–4749 (see this article for several 2-phenylindoles).

[17] V.I. Boev, L.V. Snegur, V.N. Babin, Y.S. Nekrasov, Russ. Chem. Rev. 66 (1997) 613–636.

[18] M. Henry, S. Briolant, A. Zettor, S. Pelleau, M. Baragatti, E. Baret, J. Mosnier, R. Amalvict, T. Fusai, C. Rogier, B. Pradines, Antimicrob. Agents Chemother. 53 (2009) 1926–1930.

[19] Labelling of the atoms:



[20] For the preparation of the 2-(2-piridyl) derivative 14, the acidic aqueous phase was neutralized with saturated aqueous $NaHCO_3$ solution, prior extraction with dichloromethane.

[21] T. Mosmann, J. Immunol. Methods 65 (1983) 55–63.

[22] C. Matito, F. Mastorakou, J.J. Centelles, J.L. Torres, M. Cascante, Eur. J. Nutr. 42 (2003) 42–49.