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LETTER

One-pot microwave-assisted synthesis and antimalarial activity of ferrocenyl benzodiazepines†

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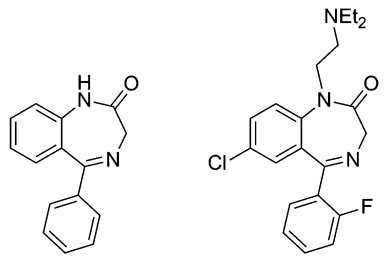
An efficient synthesis of 1,4-benzodiazepin-2-ones is described by condensation between 2-aminobenzophenone and Boc-protected amino acids *via* microwave-assisted irradiation. This produces higher yields in shorter reaction times than with traditional methods. The antiplasmodial activity of the corresponding ferrocenyl benzodiazepines was evaluated *in vitro* against *Plasmodium falciparum* F32 (chloroquine-sensitive) and FCB1 and K1 (chloroquine-resistant) strains and gabonese clinical isolates.

Benzodiazepine (BZD) derivatives have received significant attention, as their core is indeed a "privileged scaffold" found in active compounds against a variety of target types.[1] Particularly, the ability of 1,4-benzodiazepin-2-ones to bind to cholecystokinin (CCK)[2] and central benzodiazepine receptors[3] has been widely described. The benzodiazepine scaffold is also found in neurokinin-1 antagonists as enzyme inhibitors such as γ-secretase[4] and farnesyl protein transferase inhibitors.[5] Some 1,4-benzodiazepine derivatives show antiproliferative properties on tumor cell lines.[6] They have also been proven to be efficient peptidomimetic of *Plasmodium falciparum* falcipain-2 inhibitors.[7] It also appears that flurazepam (Fig. 1), an agonist of BDZ receptors, is effective against the chloroquine- and mefloquine-resistant Dd2 strain of *Plasmodium falciparum*.[8] Moreover, it has been reported that malaria infection reduces the binding capacity of benzodiazepine receptors.[9]

Our interest in the search for new antiplasmodial drugs has been focused on the synthesis of ferrocenyl 1,4-benzodiazepin-2-ones in which the aminoethyl group has been replaced by the lipophilic entity of ferrocene. Indeed, a bioorganometallic approach to cancer and malaria therapeutics is a growing area of organometallic chemistry.[10] The high lipophilicity of ferrocene and its electrochemical behavior render it very attractive for drug design. Particularly, ferroquine (FQ, SSR97193), an antimalarial molecule with a ferrocenyl moiety inserted within the side chain of chloroquine, is currently being developed by Sanofi-Aventis and entered phase II clinical trials in association with artesunate.[11]



1,4-Benzodiazepin-2-one Flurazepam

Fig. 1 Structures of 1,4-benzodiazepin-2-one and flurazepam.

Many combinatorial syntheses based on this scaffold have been reported in the literature. In particular, a general way to build the ring skeleton of 1,4-benzodiazepin-2-ones is *via* reactions between protected amino acids and an aryl moiety.[12] In other procedures, 2-aminobenzophenone was left to react with halogenoacetylhalide to produce the halogenoacetamido followed by condensation with ammonia.[13] Only one report has described a one-pot protocol for the synthesis of 5-phenyl-1,4-benzodiazepin-2-one derivatives using ammonium hydroxide solution with K_2CO_3 instead of liquid ammonia.[14] This procedure requires a reaction time of 16 hours.

Microwave-Assisted Organic Synthesis (MAOS) has become increasingly popular in recent years to improve the yield and/or to shorten reaction times in a large variety of synthetic transformations. Microwave heating of closed reaction vessels is a highly energy efficient heating technique. In developing a strategy towards the synthesis of novel ferrocenyl antimalarial drugs,[15] we applied microwave technology to a one-pot synthesis of 1,4-benzodiazepin-2-ones. Herein we present our preliminary results on the *in vitro* antimalarial activity of ferrocenyl benzodiazepines against *Plasmodium* strains and gabonese clinical isolates.

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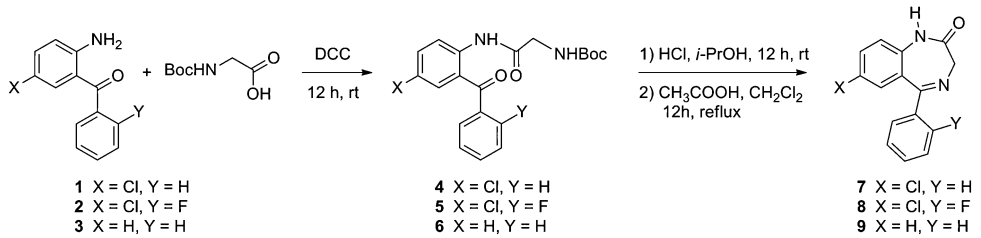


Scheme 1 Synthesis of 1,4-benzodiazepin-2-ones *via* conventional heating.

Benzodiazepines **7–9** were synthesized by the procedure outlined in Scheme 1. Peptidic coupling of substituted 2-aminobenzophenones **1–3** with protected glycine in the presence of dicyclohexylcarbodiimide (DCC) gives amides **4**, **5** and **6** in 88, 70 and 74% yields, respectively, after purification by column chromatography. The Boc-protecting group was removed by treatment with hydrochloric acid in isopropanol. Finally, benzodiazepines **7–9** were obtained by cyclization using 5% acetic acid in CH_2Cl_2 in 87–89% global yield for the two steps.[16]

With the aim to increase the yields, whilst shortening the reaction times, we decided to exploit microwave irradiation as a heating source. Using 2-amino-5-chlorobenzophenone **1** as a model substrate, various reaction conditions were tested to obtain benzodiazepine **7**. Results and conditions are summarized in Table 1.

In a general procedure, 2-amino-5-chlorobenzophenone **1** and Boc-glycine were placed in a microwave vial in the presence of a coupling reagent and a solvent. The vessel was hermetically sealed with a removable fitted cap. Heating was maintained for an appropriate period. Trifluoroacetic acid was then added to the mixture for an additional 20 min. Optimization was performed for the first step.

When an equimolar amount of **1** and Boc-glycine, in the presence of DCC, were irradiated without solvent for 5 or 10 min, no reaction occurred (entries 1 and 2). Increasing the temperature and reaction times for the first step resulted in formation of benzodiazepine **7** in only 31% yield (entry 3).

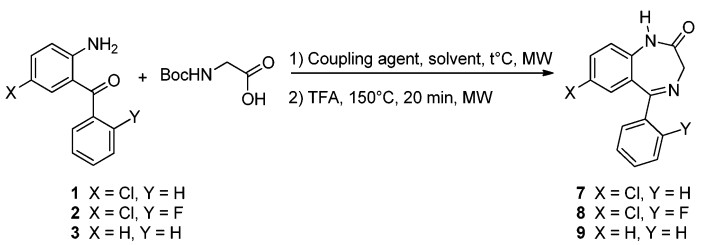
To improve the yield, several experimental conditions were tested such as temperature, solvent, coupling reagent and time. A higher yield of 86%, for **7**, is obtained when the reaction is performed using toluene as the solvent and DCC as the coupling reagent at 150 °C for 30 min (entry 6). Increasing the reaction temperature induced a lower yield (entry 5). Alternative organic solvents, including dimethylformamide and dimethylsulfoxide, were unsatisfactory due to the formation of a by-product derived from solvent decomposition (entries 7 and 8). The use of other coupling reagents such as EEDQ, EDCI and PyBOP caused a decrease in the yield (entries 9, 10 and 11).

Using the conditions reported in entry 6 for aminoketones **2** and **3**, 1,4-benzodiazepin-4-ones **8** and **9** were obtained in 80 and 83% yields, respectively, after purification by column chromatography (entries 12 and 13).

When compared to the conventional heating process, microwave irradiation has given higher yields in shorter reaction times as reported in Table 2.

Alkylation of benzodiazepines **7–9** with the ferrocenylmethyltrimethyl ammonium iodide **10** in the presence of potassium *tert*-butoxide has afforded ferrocenylmethyl

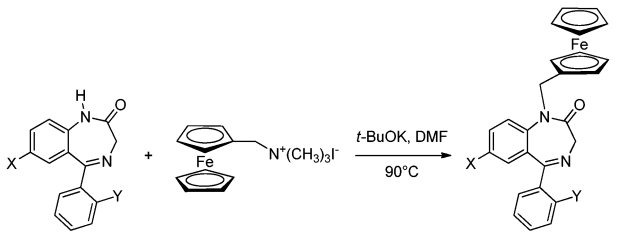
Table 1 Synthesis of benzodiazepines *via* a microwave procedure



Entry	Aminoketone	Coupling reagent	Temperature/°C	Time of first step/min	Solvent	Yield (%)
1	**1**	DCC	100	5	None	0
2	**1**	DCC	120	10	None	0
3	**1**	DCC	150	20	None	31
4	**1**	DCC	150	20	Toluene	69
5	**1**	DCC	170	20	Toluene	35
6	**1**	DCC	150	30	Toluene	86
7	**1**	DCC	150	30	DMF	21
8	**1**	DCC	150	30	DMSO	30
9	**1**	EEDQ	150	30	Toluene	31
10	**1**	PyBOP	150	30	Toluene	10
11	**1**	EDCI	150	30	Toluene	41
12	**2**	DCC	150	30	Toluene	80
13	**3**	DCC	150	30	Toluene	83

Table 2 Comparison of yields between the conventional heating method and the microwave irradiation method for benzodiazepine synthesis

Benzodiazepine	Conventional heating yield (%)	Microwave irradiation yield (%)
7	76	86
8	61	80
9	66	83



7 X = Cl, Y = H
8 X = Cl, Y = F
9 X = H, Y = H

10

11 X = Cl, Y = H
12 X = Cl, Y = F
13 X = H, Y = H

Scheme 2 Synthesis of ferrocenylmethyl benzodiazepines **11–13**.

Table 3 Comparison of yields between the conventional heating method and the microwave irradiation method for alkylation of benzodiazepines

Ferrocenyl benzodiazepines	Conventional heating yield (%)	Microwave irradiation yield (%)
11	68	71
12	78	72
13	84	34

benzodiazepines **11–13** in 68–84% yield (Scheme 2). An attempt to increase these yields *via* microwave methods was made. However, the resulting yields are lower or equal to conventional heating (Table 3).

The three ferrocenyl benzodiazepines were evaluated for their antimalarial activity *in vitro* upon the chloroquine-sensitive F32 (IC_{50} CQ = 0.019 μM) and resistant FCB1 (IC_{50} = 0.111 μM) and K1 (IC_{50} = 0.157 μM) *P. falciparum* strains. These benzodiazepines were also tested on two CQ-resistant clinical isolates from Franceville/Gabon. The potencies of the ferrocenyl compounds, as indicated by their IC_{50} values, are summarized in Table 4. All tested compounds exhibited modest activities on the CQ-sensitive F32, CQ-resistant FCB1 and K1 strains with IC_{50} ranging from 1.4 to 9.2 μM. A decrease of the antimalarial activity was observed on the CQ-resistant K1 strain and the clinical isolate 23130 with higher IC_{50} values (5.5 to 10 μM). The best biological activities have been obtained on the CQ-resistant clinical isolate 23145 with IC_{50} of 1 μM for benzodiazepine **12** and IC_{50} of 0.5 μM for **13**.

The three ferrocenyl benzodiazepines were subjected to cytotoxic evaluation against MRC-5 cells employing the MTT colorimetric method and values of 10 μM have been obtained (Table 4). These compounds provided a selectivity index calculated on K1 strain (ratio CC_{50}/IC_{50}) of 1–1.8, too low for potential development as drug candidates.

In conclusion, a convenient and efficient synthesis of 1,4-benzodiazepin-2-ones has been developed with microwave heating. Short reaction times and simple procedures and purifications make this method applicable for other benzodiazepine syntheses. The ferrocenyl benzodiazepines in particular display significant antiplasmodial activity against the *P. falciparum* F32 CQ-sensitive and FCB1 and K1CQ-resistant strains with IC_{50} ranging from 1 to 10 μM. Thus, the synthesis of ferrocenyl benzodiazepines bearing varied substituents on the ferrocenyl entity is currently underway in our laboratory.

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Experimental

Syntheses

General procedure for preparation of 7–9 by a microwave-assisted method. Substituted 2-aminobenzophenone (0.126 mmol), DCC (0.126 mmol, 0.026 g) and *N*-Boc-glycine (0.126 mmol, 0.022 g) in toluene (400 μL) were placed in a 10 mL microwave tube equipped with a magnetic stirrer. The sealed tube was placed in the cavity of the microwave reactor and irradiated for 20 min at 150 °C. Trifluoroacetic acid (600 μL, 7.9 mmol) was then added to the mixture and the reaction vessel was irradiated

Table 4 *In vitro* antiplasmodial activity against F32, FCB1 and K1 *P. falciparum* strains and gabonese clinical isolates[a] and cellular cytotoxicity[b] of ferrocenyl benzodiazepines **11–13**

In vitro activity IC_{50} (μM)						Cytotoxicity CC_{50}/μM
BDZ	F32	FCB1	K1	Isolate 23130	Isolate 23145	MRC-5 cellls
11	1.4	1.4	6.4	7	9	10
12	4	1.4	5.5	7	1	10
13	2	2.4	9.2	10	0.5	10
CQ[c]	0.019	0.111	0.157	0.100	0.095	NT[d]
FQ[c]	0.029	0.020	0.031	NT	NT	NT
ART[c]	0.031	0.018	0.029	NT	NT	NT

[a] The results are expressed as IC_{50} values at least one experiment for F32, three independent experiments for FCB1, two experiments for K1 and one experiment in triplicate for clinical isolates. [b] The cytotoxic activity was assayed *in vitro* on MRC-5 cell line using the MTT assay. [c] CQ = chloroquine, FQ = ferroquine, ART = artemisinine. [d] NT: not tested.

at 150 °C for 20 min. The solution was neutralized by an aqueous 6 N NaOH solution and extracted with dichloromethane (3 × 3 mL). The organic layers were dried over $MgSO_4$ and evaporated. The residue was purified using column chromatography (eluent: petroleum ether/diethyl ether: 7/3).

General procedure for ferrocenyl benzodiazepine synthesis. To a solution of benzodiazepines **7–9** (0.636 mmol) in freshly distilled DMF (10 mL) was added *t*-BuOK (0.713 g, 0.636 mmol) at 0 °C. After stirring for 30 min at 0 °C, ferrocenylmethyltrimethyl ammonium iodide **10** (0.169 g, 0.438 mmol) in DMF (5 mL) was added to the mixture at 20 °C. The solution was heated at 150 °C for 4 h under N_2. 1 M HCl solution was then added until neutralization and the mixture was extracted by CH_2Cl_2 (3 × 15 mL). The organic layers were dried over $MgSO_4$ and evaporated. The residue was purified using column chromatography (eluent: ethyl acetate/petroleum ether: 5/5).

7-Chloro-1,3-dihydro-1-ferrocenylmethyl-5-phenyl-2H-1,4-benzodiazepin-2-one (11). Yield 68%. Mp 184 °C. δ_H (300 MHz, $CDCl_3$) 7.37 (3H, m, ArH), 7.27 (4H, m, ArH), 7.06 (1H, m, ArH), 5.12 (1H, d, *J* 14.0 Hz, CH_2Fc), 4.70 (1H, d, *J* 10.3 Hz, CH_2), 4.41 (1H, d, *J* 14.0 Hz, CH_2Fc), 4.09 (5H, s, Cp'), 3.97 (4H, m, Cp), 3.64 (1H, d, *J* 10.3 Hz, CH_2); δ_C (75.5 MHz, $CDCl_3$) 169.1, 168.2, 140.7, 138.2, 132.0, 131.0, 130.5, 129.5, 129.4, 128.2, 124.4, 69.4, 68.6, 67.9, 56.9, 46.2. rt_{LCMS} 3.58 MS 368.9. Found: C, 66.35; H, 4.57; N, 5.96%. $C_{26}H_{21}ClFeN_2O$ requires C, 66.62; H, 4.52; N, 5.98%.

7-Chloro-1,3-dihydro-1-ferrocenylmethyl-5-(-2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one (12). Yield 78%. Mp 110 °C. δ_H (300 MHz, $CDCl_3$) 7.37–7.30 (3H, m, ArH), 7.29 (1H, td, *J* 9.1 and 3.0 Hz, ArH), 7.10 (1H, td, *J* 7.1 and 3.0 Hz, ArH), 6.99 (1H, s, ArH), 6.97–6.95 (1H, m, ArH), 5.05 (1H, d, *J* 14.2 Hz, CH_2Fc), 4.78 (1H, d, *J* 10.5 Hz, CH_2), 4.61 (1H, d, *J* 14.1 Hz, CH_2Fc), 4.07–3.96 (3H, m, Cp), 4.05 (5H, s, Cp'), 3.98 (2H, m, Cp), 3.67 (1H, d, *J* 10.5 Hz, CH_2); δ_C (75.5 MHz, $CDCl_3$) 168.1, 165.8, 140.1, 132.2, 1322, 131.5, 131.1, 130.0, 128.4, 124.3, 124.1, 116.4, 116.1, 69.7, 69.1, 68.7, 68.1, 57.0, 46.6. rt_{LCMS} 3.51 MS 486.9. Found: C, 63.99; H, 4.13; N, 5.65%. $C_{26}H_{20}ClFFeN_2O$ requires C, 64.16; H, 4.14; N, 5.76%.

1,3-Dihydro-1-ferrocenylmethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (13). Yield 84%. Mp 215 °C. δ_H (300 MHz, $CDCl_3$) 7.49 (2H, m, ArH), 7.42–7.31 (5H, m, ArH), 7.28 (2H, m, ArH), 5.20 (1H, d, *J* 15.0 Hz, CH_2Fc), 4.70 (1H, d, *J* 10.1 Hz, CH_2), 4.53 (1H, d, *J* 15.0 Hz, CH_2Fc), 4.16 (5H, s, Cp'), 3.90 (4H, m, Cp), 3.67 (1H, d, *J* 10.2 Hz, CH_2); δ_C (75.5 MHz, $CDCl_3$) 172.2, 171.2, 139.4, 138.8, 131.7, 131.3, 130.3, 129.7, 128.7, 127.2, 123.3, 121.2, 69.7, 69.1, 68.7, 68.7, 68.1, 57.0, 55.7. rt_{LCMS} 3.31 MS 434.9. Found: C, 71.12; H, 5.23; N, 6.33%. $C_{26}H_{22}FeN_2O$ requires C, 71.40; H, 5.11; N, 6.45%.

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