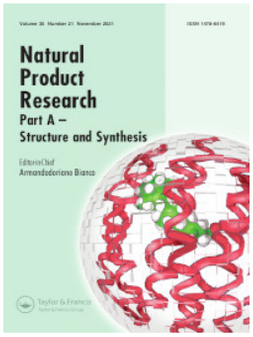

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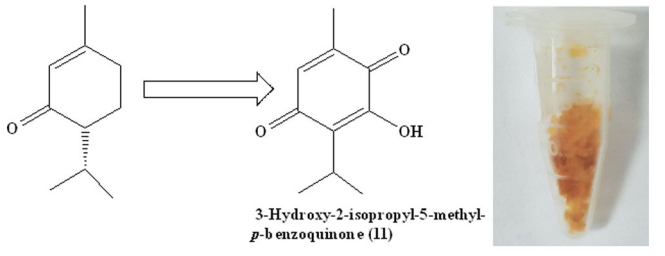
# Synthesis, structural assignments and antiinfective activities of 3-*O*-benzyl-carvotacetone and 3-hydroxy-2-isopropyl-5-methyl-*p*-benzoquinone

Veronica M. Masila[a], Albert J. Ndakala[b], Robert Byamukama[a], Jacob O. Midiwo[b], Rahab W. Kamau[c], Mei Wang[d], Mallika Kumarihamy[d], Jianping Zhao[d], Matthias Heydreich[e] and Ilias Muhammad[d]

[a]Department of Chemistry, College of Natural and Applied Sciences, Makerere University, Kampala, Uganda; [b]Department of Chemistry, School of Physical Sciences, University of Nairobi, Nairobi, Kenya; [c]Department of Chemistry, College of Natural and Applied Sciences, University of Dar es Salaam, Dar es Salaam, Tanzania; [d]National Centre for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, Mississippi, USA; [e]Institut für Chemie, Universität Potsdam, Potsdam, Germany

**ABSTRACT**

In an attempt to synthesize carvotacetone analogues, new 3-*O*-benzyl-carvotacetone (**10**) and previously reported 3-hydroxy-2-isopropyl-5-methyl-*p*-benzoquinone (**11**) were synthesized from piperitone (**7**). In this work, we describe the synthesis of **10** and other analogues from **7**. Luche reduction of **7** to *cis*-piperitol (**8**), followed by benzylation yielded 3-*O*-benzyl-piperitol (**9**). Riley oxidation of **9** afforded corresponding ketone **10**, **11** and 3-benzyloxy-4-isopropylcyclohex-1-enecarbaldehyde (**12**). Structures of these compounds were determined based on NMR, IR and LC-MS spectral data. Compound **11**, exhibited antiplasmodial activities against chloroquine-sensitive (D6) and resistant (W2) strains of *Plasmodium falciparum* with $IC_{50}$ values of 0.697 and 0.653 μg/mL, respectively. In addition, compound **11** was active against *Cryptococcus neoformans* with an $IC_{50}$ value of 3.11 μg/mL, compared to reference standard fluconazole ($IC_{50}$ value of 1.87 μg/mL), while **10** and **12** were inactive against both organisms. This is the first report of the antiplasmodial and anticryptococcal activity of compound **11**.

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CONTACT Veronica Masila masilaveronica@gmail.com

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## 1. Introduction

Malaria is a parasitic disease that affects approximately 219 million and kills 435,000 people each year world wide, majority being children under the age of 5 years and pregnant women (WHO 2018). The disease is life-threatening and is currently managed by several drugs of plant origin or their derivatives such as quinine, mefloquine, chloroquine and artemisinin (White 2007). The *P. falciparum* parasites are reported to have developed resistance against some of these drugs (Price et al. 2004). Also, the quinolines (quinine, chloroquine and mefloquine) have been reported to cause cardiotoxicity (White 2007), hence the need to identify or develop new antimalarial drugs which are affordable, less toxic and with different mechanism of action towards the *P. falciparum* parasites.

Cryptococcosis, on the other hand, results from a fungal infection of the central nervous system in immunocompromised and immunocompetent people by *Cryptococcus neoformans* (Idnurm et al. 2005). One million cases of Cryptococcal meningitis have been reported annually worldwide with over half a million deaths estimated in endemic areas of sub-Saharan Africa (Park et al. 2009). Commonly used treatments include the use of amphotericin B and fluconazole as the key antifungal agents for inductive treatment with the former considered toxic and the latter more effective but with severe side effects (Mitchell and Perfect 1995; Sar 2004). Other antifungal agents such as allylamines and nystatin are reported to be insufficiently absorbed and too toxic (Sar 2004), hence the search for new antifungal agents which are less toxic is highly desirable.

Carvotacetones are monoterpene cyclohexanone derivatives mainly isolated from fungi, mushrooms, bacteria and worms (Collu et al. 2008). Plants mainly from the genus *Sphaeranthus,* have also been reported to contain carvotacetone derivatives (Figure 1) (Jakupovic et al. 1990; Zdero et al. 1991; Machumi et al. 2012; Tran et al. 2019). Some of these cyclic unsaturated monoterpenes exhibit antimicrobial, antiplasmodial, antiproliferative and antitumor activities (Marco-Contelles et al. 2004; Machumi et al. 2012; Tran et al. 2019). They have been reported to be cytotoxic against human solid tumor cells (Machumi et al. 2012) and other human cancer cell lines (Tran et al. 2018). The cyclohexenone core of these compounds is considered a potential new class of small molecule "pharmacophore" for antitumor drug leads which targets multi-drug resistant (MDR) tumours (Collu et al. 2008).

3-Acetoxy-5,7-dihydroxycarvotacetone (**4**) has been reported to possess anti-plasmodial activity with $IC_{50}$ values of 0.60 and 0.68 μg/mL against chloroquine sensitive (D6) and chloroquine resistant (W2) strains of *P. falciparum,* respectively (Machumi et al. 2012). In addition, compound **4** and its analog **3** also displayed cytotoxicity to various human solid tumor cells (Machumi et al. 2012). 3-Angeloyloxy-5-[3-chloro-2-hydroxy-2-methylbutanoxy]-7-hydroxycarvotacetone (**5**) and 5-angeloyloxy-7-hydroxy-3-tigloyloxycarvotacetone (**6**) displayed activities against four human cancer cell lines (acute lymphoblastic leukemia (CCRF-CEM), breast adenocarcinoma (MDA-MB-231), glioblastoma astrocytoma (U-251) and colon carcinoma (HCT-116)) with $IC_{50}$ values between 1.44-6.97 and 3.57-6.86 μg/mL, respectively (Tran et al. 2018). The synthetic carvotacetone analogue (**1**) had an $IC_{50}$ value of 3.52 μg/mL towards non-small cell lung cancer cell lines (Christou et al. 2013).

In continuation of our previous report on carvotacetones from *S. bullatus* (Machumi et al. 2012), the anti-plasmodial and cytotoxic activities of these small molecules had prompted us to synthesise previously unreported benzylated carvotacetone analogues in order to evaluate their bioactivities.

In this paper, we describe a short strategy to prepare 3-hydroxy-2-isopropyl-5-methyl-*p*-benzoquinone (**11**) and the 3-*O*-benzyl-carvotacetone (**10)** together with other analogues from piperitone (**7**), predominantly (*R*) (-) form. The spectroscopic characterization, using full NMR and MS data of the synthetic compounds and their intermediates are also discussed. In addition, the anti-plasmodial and the antifungal activities for these compounds are also reported here.

## 2. Results and discussion

### 2.1. Synthesised compounds

The synthesis began from piperitone (**7**), predominantly (*R*) (-) form, which was subjected to Luche reduction (Fruhmann et al. 2014) to form *cis*-piperitol (**8**) in 78% yield. The identity of **8** was readily confirmed on the basis of its $^{1}$H and $^{13}$C NMR spectral data. Both the $^{1}$H and $^{13}$C were consistent with literature values for *cis* piperitol (Wińska et al. 2010).

*Cis*-piperitol was then protected as the benzyl ether. Benzylation of **8** was carried out with benzyl bromide using NaH as a base. Chromatographic purification yielded a pale-yellow oil of 3-*O*-benzyl-piperitol (**9**), 5.2 g (58%). The success of the reaction was confirmed by NMR spectral data. The $^{1}$H NMR spectrum showed close similarity to compound **8**, presence of an isopropyl unit $(CH_3)_2CH$-, $\delta$ 0.98 (*d*, $J = 6.5\,Hz$) and $\delta$ 1.0 (*d*, $J = 6.5\,Hz$) , methine proton at $\delta$ 1.86 (*m*), another methine proton at $\delta$ 1.09 (*m*), two sets of methylene protons at $\delta$ 2.02/2.07 (*dd*), $\delta$ 1.63 (*m*) and a methyl attached to an olefinic carbon was observed at $\delta$ 1.77 (*s*). The major difference was the presence of an additional set of oxy-methylene protons at $\delta$ 4.73 and $\delta$ 4.49 integrating for one proton each appearing as a doublet with a *J* value of 11.7 *Hz* and three sets of aromatic protons observed at $\delta$ 7.39 (*m*), $\delta$ 7.36 (*m*) and $\delta$ 7.28 (*m*).

Most of the $^{13}$C NMR data resembled that of compound **8** with the characteristic peaks of the isopropyl moiety present. An additional deshielded oxymethylene carbon appearing at $\delta$ 70.1, a quaternary carbon at $\delta$ 139.6 and three sets of aromatic carbons at $\delta$ 128.2, 127.5 and $\delta$ 127.2 were notable. In the HMBC spectrum, the oxymethine proton at $\delta$ 3.89 (H-3), correlated well with the oxy-methylene carbon at position 7′, methylene carbon at position five, olefinic carbons at position two and one, (H-3 $\rightarrow$ C-7′, C-5, C-2, C-1), with proton H-7′ showing strong correlations with oxymethine carbon at position three and aromatic carbons, (H-7′ $\rightarrow$ C-3, C-1′, C-2′/C-6′). This was a very clear indication that the benzyl ether group had been introduced to the *cis*-piperitol to form 3-*O*-benzyl-piperitol (**9**).

Allylic oxidation of **9** proceeded under Riley oxidation conditions using $SeO_2$ in dioxane/formic acid (Nakamura and Nakada 2013) to provide the corresponding allylic ketone **10** as a reddish-brown oil in 50% yield, a benzoquinone **11** (36%), previously synthesised (Kende et al. 1974; Santos et al. 2003) and isolated from *Antiphiona pinnatisecta* (Zdero and Bohlmann 1989), and an aldehyde **12** (10%). The IR spectrum

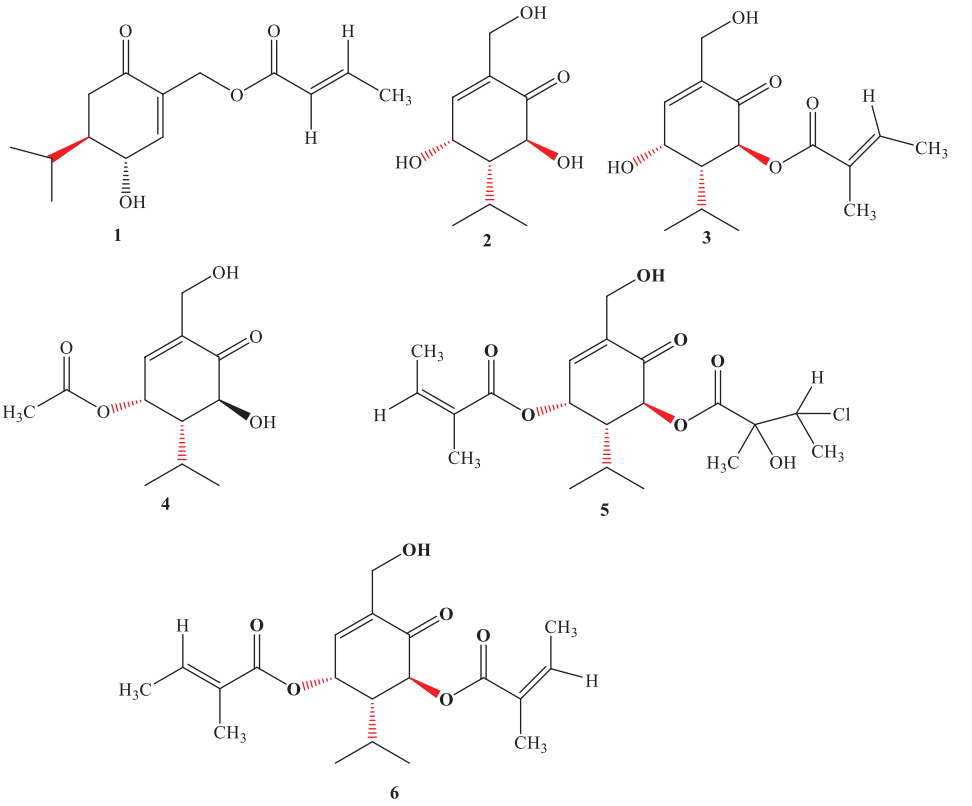


Figure 1. Synthetic carvotacetone (**1**) (Christou et al. 2013) and isolated carvotacetones from *S. bullatus* (**2–4**) (Machumi et al. 2012) and *S. africanus* (**5–6**) (Tran et al. 2018).

showed characteristic absorption bands of an ether, C-O-C at 1039.63 $cm^{-1}$ and a carbonyl at 1658.78 $cm^{-1}$.The $^{1}$H-NMR and $^{13}$C NMR spectra were similar to that of compound **9**. However, the methylene proton signal appearing at $\delta$ 2.02/2.07 disappeared together with the peak for the carbon correlating to it at $\delta$ 31.7 at position six. This methylene carbon had been replaced with a signal appearing at $\delta$ 198.1 ppm for the carbonyl group. The methyl protons at position seven $\delta$ 1.83 showed strong correlations with the keto group at position six, and two olefinic carbons at position one and two, (H-7 $\rightarrow$ C-1, C-2 and C-6), with the proton at position two correlating with H-2 $\rightarrow$ C-4 and C-6. The compound was therefore identified as a ketone, 3-*O*-benzyl-carvotacetone (**10**).

Compound **12** was synthesised as a reddish-brown paste having a molecular formula of $C_{17}H_{22}O_2$ and a molecular ion peak at *m/z* 259.2. The $^{1}$H and $^{13}$C NMR bore a resemblance to those of compound **9** except for an additional characteristic peak of an aldehydic proton appearing at $\delta$ 9.54, (*s*) with a HSQC correlation to the peak at $\delta$ 194.7. It was also noted that the peak for the methyl at $\delta$ 1.77 (s) and its corresponding carbon at $\delta$ 23.7 disappeared. The position of the carbonyl group of the aldehyde was confirmed based on HMBC correlation of the de-shielded aldehydic proton $\delta$ 9.54 with C-6, C-2 and C-1. In addition, H-6 and H-2 strongly correlated with the carbonyl

group at position seven. Hence, the compound was deduced to be an aldehyde, 3-benzyloxy-4-isopropylcyclohex-1-enecarbaldehyde (**12**).

### 2.2. Anti-plasmodial and antifungal activities

Compound **11** displayed good activity against *P. falciparum* parasites with $IC_{50}$ values of 0.697 and 0.653 μg/mL against chloroquine sensitive (D6) and chloroquine resistant (W2) strains, respectively. Chloroquine which was used as the standard drug had $IC_{50}$ values of 0.01 and 0.14 μg/mL against D6 and W2, respectively. However, all the other compounds were found to have $IC_{50} > 4.76$ μg/mL against *P. falciparum*. In addition, compound **11** was found to be selectively active against *C. neoformans* with an $IC_{50}$ value of 3.11 μg/mL, compared to fluconazole ($IC_{50}$ value of 1.87 μg/mL), a reference standard, while compounds **8**, **10** and **12** were inactive against *C. neoformans* ($IC_{50}$ value of >20, >20 and 15.77 μg/mL), respectively. This appears to be the first report of the antiplasmodial and anticryptococcal activity of compound **11**.

## 3. Experimental

### 3.1. Instruments and chemicals

All reagents and other chemicals were purchased from Merck, Loba Chemie and Santa Cruz and used without further purification. Reactions requiring anhydrous conditions were performed under nitrogen. The reactions were done in glassware that were dried in an oven (110 °C) for at least 2 hours and allowed to cool under nitrogen. Solvents for column chromatography were distilled in the laboratory in glass apparatus. Chromatographic separation was done on silica gel 60-120 mesh. Thin layer chromatography was performed on Merck silica gel 60 $F_{254}$ TLC plates and visualised under 254 nm UV lamp and 0.5% $KMnO_4$ as a visualizing agent.

$^{1}$H-NMR (500 MHz) and $^{13}$C-NMR (125 MHz) were recorded on an Agilent DD2-500 NMR spectrometer (Santa Clara, CA, USA) with tetramethyl silane as an internal standard. The high resolution mass spectrum was acquired via LCMS (Agilent).

### 3.2. Synthesis of compound 8, 9, 10, 11 and 12

All the compounds were synthesised as illustrated in Figure 2.

#### 3.2.1. Luche reduction of piperitone (7)

Piperitone (17.50 g) and $CeCl_3.7H_2O$ (21.44 g) in a 250 mL reaction flask were dissolved in 100 mL of MeOH. $NaBH_4$ (4.36 g) was added to the reaction mixture within five minutes with constant stirring. The progress of the reaction was monitored using TLC with 0.5% $KMnO_4$ as a visualizing agent. TLC analysis (EtOAc:*n*-hexane = 1:9) revealed total conversion of the starting material after 24 hours. The reaction mixture was concentrated under reduced pressure on a rotary evaporator. Work up was done by partitioning the concentrate in a mixture of 200 mL of ethyl acetate and 50 mL of $H_2O$. The organic phase was dried over $Na_2SO_4$, filtered, concentrated under reduced pressure

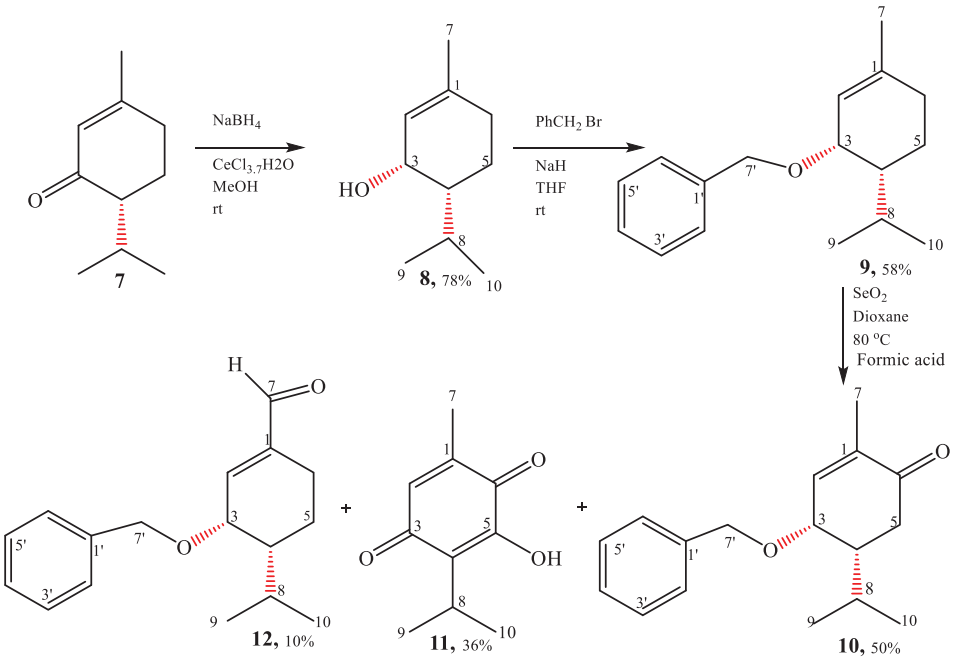


Figure 2. Synthetic route to compounds **8**, **9**, **10**, **11** and **12.**

and subjected to gradient column chromatography to provide a pale-yellow oil (**8**), (13.6 g, 78%).

### *3.2.2. Benzylation of (8)*

*Cis*-piperitol **8**, (9.0 g) was dissolved in 30 mL of anhydrous THF under $N_2$ in a 100 mL round bottomed flask. Sodium hydride (14.29 g, 60% dispersion in mineral oil) , was added and stirred at room temperature for 30 minutes. Benzyl bromide (9 mL) was added dropwise to the reaction mixture and left to stir at room temperature for 36 hours. Methanol (5 mL) was used to quench the reaction. Work up was done by concentrating the mixture on a rotary evaporator, dissolving it in 100 mL of $CH_2Cl_2$ and washing with 30 mL of $H_2O$ twice. The organic phase was dried over $Na_2SO_4$, filtered, concentrated under reduced pressure and purified by column chromatography using ($CH_2Cl_2$/*n*-hexane 0.5:9.5) to provide a colourless oil of **9** (5.2 g, 58%).

### *3.2.3. Riley oxidation of 9 to 10, 11 and 12*

3-*O*-benzyl-piperitol **9**, (2.0 g) in 1,4 dioxane/HCOOH (25/1) was placed in a 100 mL round bottomed flask. Selenium dioxide (1.2 g) was added at room temperature and stirred at 80 °C for 3 days. The mixture was then concentrated on a rotary evaporator. The concentrate was partitioned in a mixture of water (20 mL) and $CH_2Cl_2$ (100 mL) using separatory funnel. The aqueous layer was extracted twice with 200 mL of $CH_2Cl_2$. The combined organic extract was dried over $Na_2SO_4$, filtered, concentrated under reduced pressure and purified by column chromatography using (EtOAc/*n*-hexane = 1:9) to provide 1000 mg (50%) of **10**, 700 mg (35.5%) of **11** and 200 mg (10%) of **12**.

## 4. Spectroscopic Data

3-*O*-benzyl-piperitol (**9**): Pale yellow oil. $^{1}H$ and $^{13}C$ NMR ($CDCl_3$, 500 and 125 MHz): see Table S1. IR: 1062.78 $cm^{-1}$, MS: *m/z* 243.4.

3-*O*-benzyl-carvotacetone (**10**): Reddish brown paste. $^{1}H$ and $^{13}C$ NMR ($CDCl_3$, 500 and 125 MHz): see Table S9. IR: 1658.78 $cm^{-1}$, 1039.63 $cm^{-1}$, *m/z* 259.2.

3-Benzyloxy-4-isopropylcyclohex-1-enecarbaldehyde (**12**): Reddish brown paste. $^{1}H$ NMR ($CDCl_3$, 600 MHz, ppm): $^{1}H$ and $^{13}C$ NMR ($CDCl_3$, 500 and 125 MHz): see Table S17. IR:1681.93 $cm^{-1}$, 1056.99 $cm^{-1}$, *m/z* 259.2.

### *4.1. Antiplasmodial and antifungal activities*

The antiplasmodial assay was assessed *in vitro* by a colorimetric method that determines the parasitic lactate dehydrogenase (pLDH) activity (Makler and Hinriches 1993; Makler et al. 1993), in accordance with those reported previously (Samoylenko et al. 2009).

All the organisms in the antimicrobial assay were obtained from the American Type Culture Collection (Manassas, VA). Susceptibility testing was performed using a modified version of the CLSI methods (NCCLS 1998, 2000a, 2000b). Drug controls ciprofloxacin, methicillin and vancomycin for bacteria and amphotericin B for yeasts and fungi were included in each assay. Susceptibility testing was performed at the National Center for Natural Products Research, University of Mississippi, as described (Samoylenko et al. 2009).

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## Disclosure statement

Authors declare no conflict of interest.

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