**Preprint Title**  First Total Synthesis of Hoshinoamides A

**Authors**  Haipin Zhou, Zihan Rui, Yiming Yang, Shengtao Xu, Yutian Shao and Long Liu

**Publication Date**  15 Sep 2021

**Article Type**  Letter

**Supporting Information File 1**  Supporting Information Hoshinoamides A.docx; 1.2 MB

**ORCID® iDs**  Haipin Zhou - https://orcid.org/0000-0003-2961-5829; Long Liu - https://orcid.org/0000-0003-0821-6992
First Total Synthesis of Hoshinoamides A

Haipin Zhou\textsuperscript{a}, Zihan Rui\textsuperscript{a}, Yiming Yang\textsuperscript{a}, Shengtao Xu\textsuperscript{a,b}, Yutian Shao \textsuperscript{a,*} and Long Liu\textsuperscript{c,*}

\textsuperscript{a}College of Materials & Chemical Engineering, Chuzhou University, Chuzhou 239000, China

\textsuperscript{b}State Key Laboratory of Natural Medicines and Department of Medicinal Chemistry, China Pharmaceutical University, 24 Tong Jia Xiang, Nanjing 210009, China

\textsuperscript{c}Taizhou Medical Hi-Tech Development Public Services Platform, Taizhou 225300, China;

Email: Long Liu---15102209730@163.com

Email: Yutian Shao ---shaoyutian22@163.com

* Corresponding author
Abstract

Hoshinoamides A, B and C, linear lipopeptides, were isolated from the marine cyanobacterium *Caldora penicillata*, with potent antiplasmodial activity against chloroquine-sensitive *Plasmodium falciparum*. Herein, we describe the first total synthesis of Hoshinoamides A. Our synthetic strategy uses the combined methods of solution and solid phase peptide synthesis. Liquid phase synthesis is to improve the coupling yield of L-Val$_3$ and N-Me-D-Phe$_2$. Connecting other amino acids efficiency and convergence by solid state synthesis. This synthetic strategy has good purity and high yield.

Keywords

highly methylated polypeptides; Hoshinoamides; total synthesis; antimalarial;

Introduction

Malaria is an insect-borne infectious disease caused by parasites of the genus Plasmodium, which seriously threatens human life and health$^{[1]}$. Half of the world's population is at the risk of malaria, with about 200 million new infections and killing hundreds of thousands of people each year$^{[2]}$. Current medicines for malaria include quinolone$^{[3,4]}$, folic acid antagonist$^{[5,6]}$ and artemisinin derivatives$^{[7]}$. The emergence of drug resistance makes the efficacy of these drugs decline year by year, forcing scientists to constantly search for new antimalarial drugs$^{[8-10]}$.

In recent years, Iwasaki and co-workers reported three novel linear lipopeptides natural products, Hoshinoamides A, B$^{[11]}$ and C$^{[12]}$, from a microbial metabolite of marine cyanobacterium *Caldora penicillata* (Figure 1). Hoshinoamides A and B showed potent activities against chloroquine-sensitive *Plasmodium falciparum* 3D7 with IC$_{50}$ values of 0.52 and 1.0 $\mu$M, respectively. Hoshinoamides C inhibited the growth of the malaria parasites (IC$_{50}$
0.96 μM) and African sleeping sickness (IC₅₀ 2.9 μM). Both Hoshinoamides A and B are highly methylated polypeptides containing three N-methyl amino acids: N-Me-L-Leu⁷, N-Me-D-Val⁵ and N-Me-D/L-Phe₂. Hoshinoamides C includes two N-methyl amino acids: N-Me-D-Phe₂ and N-Me-D-Ile⁵. The C-terminal is Pro methyl ester while the N-terminal polypeptide is linked to long alkyl chain amino acid Aha₈/Ana₈/Ama₇ and p-hydroxybenzoic acid Hba₈/Hba₈. Hoshinoamides have a relatively simple structure and therefore make an attractive target for further medicinal chemistry studies. To enable these new SAR studies, we would first need to develop efficient synthetic method to provide sufficient material. Hoshinoamides A shows better antimalarial activity and less cytotoxicity compared to Hoshinoamides B. Herein, we report the initial progress on the total synthesis of Hoshinoamides A. The key challenges for the total synthesis of Hoshinoamides A are the coupling of highly methylated amino acids and the purification of hydrophobic peptides.
Figure 1. a) Structures of Hoshinoamides A and B. b) Structures of Hoshinoamides C
Results and Discussion

As shown in Scheme 1, we initially tested Fmoc Solid-phase peptide synthesis (SPPS) to get 2-chlorotrityl resin-bound Pro\(_1\)-(N-Me)Phe\(_2\) dipeptide 2 under the condition of HCTU and DIPEA. Unfortunately, the N-Me coupling proceeded in low yield (<10%).

Scheme 1. Synthesis of resin-bound tripeptide 3 by SPPS

In order to improve the coupling yield of hindered peptide, we tried to condensation of Val\(_3\) with dipeptide in solution phase. Pro-Bn 5 was first coupled with Fmoc-N-Me-D-Phe-OH by the treatment of HATU and DIPEA, giving the dipeptide 6 in 83% yield (Table 1). We envisioned a sequential deprotection of Fmoc of dipeptide 6 and then coupling with Fmoc-Val-OH will deliver tripeptide 7. With this in mind, we next screened a series of coupling reagents. As shown in Table 1, the coupling reagents have a significant effect on the efficiencies of the reactions. While most of coupling reagents could give the tripeptide 7, the combination of HATU/DIPEA shown the best result, delivering 7 in 78% isolated yield (Table 1, entry 2). Only trace product could be detected while EEDQ was used as the coupling reagent. The purity of tripeptide 7 was determined by HPLC and no racemization was observed, ensuring the smooth progress of the total synthesis of Hoshinoamides A.
Table 1: Hindered Peptide coupling: Conditions and Yields

| Entry | Coupling reagent[^a] | Yield[^b] (%) | Racemization[^c] |
|-------|----------------------|---------------|------------------|
| 1     | HCTU, DIPEA          | 36            | NO               |
| 2     | HCTU, DIPEA          | 78[^d]        | NO               |
| 3     | HATU, DIPEA          | 75            | NO               |
| 4     | HATU, HOAT, DIPEA    | trace         | NO               |
| 5     | EEDQ                 | 41            | NO               |
| 6     | DIC, HOAT            | 24            | NO               |

[^a]: 0.1 mmol/L of dipeptide 6 and Fmoc-Val in DMF, 1.5 equiv coupling reagent, rt, 3 h.  
[^b]: Yield were determined by H NMR data analysis.  
[^c]: Racemization were determined by HPLC.  
[^d]: Isolated yield.

With the Tripeptide 7 in hand, we went on to construct the peptide scaffold (Scheme 2). Deprotection of the Bn groups by Pd(OH)$_2$-catalyzed hydrogenolysis gave the tripeptide 8. Treatment of 2-chlorotrityl (CTC) resin with 8 (4 equiv.) with DIPEA successfully produced the resin-bound tripeptide 3 in good yield. It should be noted unreacted 8 can be largely recovered by a quick silica gel chromatography. The N terminus of 3 was then sequentially extended with properly protected L-Gln$_4$, N-Me-D-Val$_5$, L-Ile$_6$, N-Me-L-Leu$_7$, Ana$_8$, and Hba$_9$ units to give 9-mer peptide 9 using the standard SPPS procedure. It is worth noting that, in order to increase the yield, when coupling L-Ile$_6$ and Ana$_8$, the reaction time increases, and the reaction times increase. The peptide chain was then cleaved from resin by the treatment of 0.5% TFA in DCM and removal of the Trt group with aqueous solution of TFA gave 9-mer peptide 10 in good yield after HPLC purification. The carboxylic acid of 9-mer peptide 10 was converted to ester with MeI and K$_2$CO$_3$ in DMF, delivering the final natural product.
Hoshinoamides A in 2% yield (10 mg). The spectroscopic data of synthetic Hoshinoamides A were in excellent agreement with the data previously reported for the natural product.

Scheme 2. Synthesis of Hoshinoamides A
Conclusion

In summary, we completed the first total syntheses of Hosh-inoamides A. Through the combination of the solution and solid phase peptide synthesis, Hoshinoamides A was synthesized in high efficiency. After systematic screening of the coupling reagents in solution phase, the key intermediate tripeptide 7 was obtained with high yield. The solid phase synthesis improves the entire efficiency of the synthetic route. This strategy could be applied to stereoselectively synthesize Hoshinoamides A and other highly methylated polypeptides analogues, which was helpful to further study its biological activity against malaria. Structure-and-activity and functional studies with the fluorescent-labelled analogs is currently under investigation in our lab.

Experimental

**General Experimental Procedures.** $^1$H-NMR spectra were obtained using a Bruker AVANCE AV 400 at frequencies of 400 MHz respectively in CDCl$_3$, CD$_3$OD or D$_2$O. Chemical shifts are reported in parts per million (ppm) and coupling constants in Hertz (Hz). The residual solvent peaks were used as internal standards. $^1$H-NMR data is reported as follows: chemical shift values (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and relative integral. $^{13}$C-NMR spectra were obtained using a Bruker AVANCE AV 400 at 100 MHz in CDCl$_3$, CD$_3$OD or D$_2$O. $^{13}$C-NMR data is reported as chemical shift values (ppm).

LC-MS was performed on a Thermo Scientific MSQ instrument with the spectrometer operating in positive mode. Separations on the LC-MS system were performed on two methods using a thermo accucore C18 (2.6 μm, 100 x 2.1 mm) column. Method A: Linear gradient of 10-90% CH$_3$CN/H$_2$O and 0.1% TFA over 40 min was applied at a flow rate of 1.0
mL/min and detection at 220 nm. Method B: Linear gradient of 10-90-90-10% CH₃CN/H₂O and 0.1% TFA over 10 min (10-90 vol% MeCN over 6 min, 90-90 vol% over 3 min, 90-10 vol% MeCN over 1 min) was applied at a flow rate of 1.0 mL/min and detection at 220 nm. Preparative reverse-phase HPLC was performed using Thermo Scientific Ultimate 3000 equipped with a Thermo Hypersil Gold (5 µm, 150 x 21.2 mm) column using the following buffer systems: A: 0.1% TFA in water. B: 0.1% TFA in MeCN using a 10-90-90-10% MeCN gradient (10-90 vol% MeCN over 30 min, 90-90 vol% over 10 min, 90-10 vol% MeCN over 10 min) at a flow rate of 8 mL/min.

Standard SPPS (solid phase peptide synthesis) method:

1) General procedure for coupling on resin: The loaded resin was shaken for 2 h at room temperature with a solution of the desired Fmoc-AA-OH (4 equiv), HATU/Coupling reagent (4 equiv) and DIPEA (8 equiv) in DMF (20 mL). The coupling mixture was filtered and the resin was washed with CH₂Cl₂ (10 mL x 5) and CH₃OH (10 mL x 5).

2) General procedure for deprotection of Fmoc: The loaded resin was treated with a solution of 20 vol% piperidine in DMF (20 mL) for 30 min and then filtered. The resin was washed with CH₂Cl₂ (20 mL x 5) and CH₃OH (20 mL x 5).

3) General procedure for cleavage the peptide from the resin: 0.5% TFA in DCM (20 mL) were added on the resin and the mixture was shaken for 2h before filtered. The resin was washed with CH₂Cl₂ (20 mL x 5) and CH₃OH (20 mL x 5).

Fmoc-Pro-OH (674 mg, 2 mmol) was then dissolved in a mixture of DCM (10 mL) and DMF (10 mL). DIPEA (1.7 mL, 10 mmol), 2-CTC resin (1 g) were added to this mixture and the reaction was stirred at room temperature was for 2h. The resin was filtered and washed with MeOH (3 x 20 mL), DCM (3 x 20 mL). The unreacted resin was capped with MeOH in a mixture of MeOH:DIPEA:DCM (1:2:7, 10 mL) for 3h. The resin-bound peptide was added to a mixture of 20% piperidine in DMF (20 mL), and the mixture was shaken to for 30 minutes. Then the mixture was filtered, the resin was washed with MeOH (3 x 20 mL) and DCM (3 x
20 mL). Fmoc-N-Me-D-Phe-OH (1000 mg, 2.5 mmol), HCTU (1.0 g, 2.5 mmol) and DIPEA (871 µL, 5.0 mmol) in DMF were added on the resin and the reactor was shaken for 1 h at room temperature. Then the mixture was filtered, the resin was washed with MeOH (3 x 20 mL) and DCM (3 x 20 mL) to afford the resin-bound dipeptide. The resin-bound dipeptide was added to a mixture of 20% piperidine in DMF (20 mL), and the mixture was shaken to for 30 minutes. Then the mixture was filtered, the resin was washed with MeOH (3 x 20 mL) and DCM (3 x 20 mL). Fmoc-Val-OH (848 mg, 2.5 mmol), HATU (1.0 g, 2.5 mmol) and DIPEA (871 µL, 5.0 mmol) in DMF were added on the resin and the reactor was shaken for 1 h at room temperature. The resulting tripeptide was analysed on a Thermo Scientific MSQ instrument, and few product was observed.

Fmoc-N-Me-D-Phe-Val-Pro-Bn (6). Pro-OBn.HCl (2.41 g, 10 mmol), Fmoc-N-Me-D-Phe-OH (4.01 g, 10 mmol) and DIPEA (5.2 mL, 30 mmol) was dissolved in 50 mL anhydrous DCM. HATU (5.7 g, 15 mmol) was added to the solution and the mixture was stirred at room temperature for 6 h. The reaction mixture was then washed by 1.0 M HCl (20 mL), aqueous NaHCO₃ (20 mL) and brine (20 mL). The organic phase was dried with anhydrous Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography (n-hexanes: EA=2:1) to afford dipeptide 6 (4.9 g, 83%).¹H NMR (400 MHz, Methanol-d₄) δ 7.39 – 7.27 (m, 19H), 5.20 – 5.12 (m, 4H), 4.85 (s, 6H), 4.44 (ddd, J = 13.1, 9.5, 4.8 Hz, 4H), 3.50 (ddd, J = 10.0, 7.4, 5.4 Hz, 2H), 3.31 – 3.23 (m, 4H), 3.07 (dd, J = 12.8, 10.3 Hz, 2H), 2.57 (s, 6H), 2.46 (dt, J = 9.9, 7.0 Hz, 2H), 2.03 – 1.94 (m, 2H), 1.89 – 1.71 (m, 4H), 1.48 (dddd, J = 12.5, 7.1, 5.4, 1.6 Hz, 2H). ¹³C NMR (101 MHz, MeOD) δ 171.21, 165.90, 135.71, 133.51, 129.37, 128.70, 128.24, 128.07, 127.93, 127.74, 66.74, 60.75, 59.32, 48.27, 48.06, 47.84, 47.63, 47.41, 47.21, 46.99, 46.88, 36.55, 30.88, 28.45, 23.94. HRMS: (+ESI) Calc. for C₂₂H₂₆N₂O₃: 588.2671[M+H]⁺, Found: 588.2673 [M+H]⁺.
Fmoc-Val-N-Me-D-Phe-Val-Pro-Bn (7). Dipeptide 6 (118 mg, 0.20 mmol), Fmoc-Val-OH (71 mg, 0.20 mmol) was dissolved in 10 mL anhydrous DMF. Coupling reagents was added to the solution and the mixture was stirred at room temperature for 3 h. This mixture poured onto water (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). Then washed by 1.0 M HCl (10 mL), aqueous NaHCO₃ (10 mL) and brine (10 mL). The organic phase was dried with anhydrous Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash column chromatography (n-hexanes: EA=2:1) to afford tripeptide 7. ¹H NMR (400 MHz, Chloroform-d) δ 7.75 (d, J = 7.7 Hz, 2H), 7.57 (t, J = 7.2 Hz, 2H), 7.40 – 7.17 (m, 14H), 5.72 (dd, J = 8.9, 6.5 Hz, 1H), 5.46 (d, J = 9.5 Hz, 1H), 5.23 – 5.20 (m, 1H), 5.06 (d, J = 12.2 Hz, 1H), 4.50 – 4.18 (m, 5H), 3.48 – 3.43 (m, 1H), 3.28 (dt, J = 11.3, 5.8 Hz, 2H), 3.10 (s, 1H), 2.95 – 2.86 (m, 3H), 2.21 – 2.14 (m, 2H), 1.78 – 1.62 (m, 5H), 1.28 (s, 2H), 0.76 (dd, J = 66.2, 6.8 Hz, 3H), 0.47 (dd, J = 46.7, 6.7 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.70, 171.60, 168.26, 156.39, 143.88, 141.30, 137.01, 129.54, 128.88, 128.69, 128.60, 128.50, 128.39, 128.31, 128.20, 127.72, 127.08, 126.65, 125.17, 125.08, 119.99, 77.40, 77.09, 76.77, 67.04, 66.84, 59.43, 55.87, 55.59, 47.17, 46.92, 35.00, 30.72, 30.47, 28.78, 25.25, 19.82, 16.33. HRMS: (+ESI) Calc. for C₄₂H₄₅N₃O₆: 688.3381 [M+H]⁺, Found: 688.3384[M+H]⁺.

Comparison of the effects of different coupling reagents on the reaction yield (Table 1).

Fmoc-Val-N-Me-D-Phe-Val-Pro-OH (8). Tripeptide 7 (2.3 g, 3.3 mmol) was dissolved in 30 mL of MeOH/HCOOH(v/v=9:1) and hydrogenized with Pd(OH)₂ (500 mg, 10% on carbon) under H₂ for 10 hours to remove the Bn groups. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo to give brown oil which was purified by flash chromatography (n-hexanes:EA = 2:1), affording tripeptide 8 (1.87 g, 95%) as a white foam. ¹H NMR (400 MHz, Methanol-d₄) δ 7.59 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 7.21 – 6.96 (m, 10H), 5.52 (dd, J = 43.6, 9.9, 5.6 Hz, 1H), 4.81 (s, 2H), 4.20 – 3.98 (m, 4H), 3.29 – 3.10 (m, 2H), 3.04– 2.91 (m, 4H), 2.80 – 2.67 (m, 2H), 2.62
(s, 3H), 2.01 – 1.83 (m, 2H), 1.53 (ddq, \(J = 50.8, 19.7, 6.9\) Hz, 4H), 1.13 – 1.09 (m, 2H), 0.52 – 0.45 (m, 4H). \(^{13}\)C NMR (101 MHz, MeOD) \(\delta\) 175.49, 175.06, 174.95, 173.81, 173.14, 171.16, 170.16, 167.42, 164.85, 158.64, 158.58, 158.53, 145.38, 145.35, 145.20, 145.13, 145.09, 142.88, 142.55, 138.50, 138.41, 131.03, 130.75, 130.66, 130.27, 129.77, 129.64, 129.57, 129.42, 128.86, 128.83, 128.55, 128.28, 128.21, 127.77, 127.66, 126.35, 126.29, 126.21, 125.76, 121.02, 70.63, 68.11, 68.04, 66.85, 60.78, 60.68, 59.15, 58.19, 57.76, 57.67, 57.41, 57.06, 56.41, 56.08, 49.75, 49.54, 49.32, 49.11, 48.90, 48.68, 48.47, 48.41, 48.25, 47.74, 38.96, 37.58, 37.01, 36.60, 35.79, 35.61, 33.11, 32.20, 31.89, 31.73, 31.53, 31.40, 30.88, 30.83, 30.66, 30.53, 30.39, 29.98, 29.64, 28.18, 26.97, 26.10, 23.80, 23.34, 19.88, 19.48, 18.17, 18.07, 17.64, 14.58. HRMS: (+ESI) Calc. for C\(_{35}\)H\(_{39}\)N\(_3\)O\(_6\): 598.2912 [M+H]+, Found: 598.2915[M+H]+.

Compound tripeptide 8 (1.20 g, 2 mmol) was then dissolved in a mixture of DCM (10 mL) and DMF (10 mL). DIPEA (1.7 mL, 10 mmol), 2-CTC resin (1 g) were added to this mixture and the reaction was stirred at room temperature was for 3h. The resin was filtered and washed with MeOH (3 x 20 mL), DCM (3 x 20 mL). The unreacted resin was capped with MeOH in a mixture of MeOH:DIPEA:DCM (1:2:7, 10 mL) for 5 h. Fmoc protecting group was removed following the general procedure and the remain amino acids were successively coupled using the standard SPPS method. 0.5% TFA in DCM (20 mL) were added on the resin and the mixture was shaken for 2h to cleavage the peptide from the resin. The mixture was filtered and the filtrate was concentrated \textit{in vacuo} to give a white foam. The peptide was re-dissolved in a mixture of TFA:Et\(_3\)SiH:H\(_2\)O (10 mL, 50/50/50 v/v/v). The reaction mixture was stirred for 3 h, and then concentrated \textit{in vacuo}. The crude peptide was precipitated using cold Et\(_2\)O and centrifuged at 7000 rpm to give a white solid. This solid was further purified by RP-HPLC using protocols described in the general method. Fractions were collected, concentrated and lyophilized to give nanopeptide 10 as a white solid. Nanopeptide
10 was dissolved in dry DMF (5 mL). K₂CO₃ (3.1 mg, 0.022 mmol) and MeI (3.13 mg, 0.022 mmol) was added to this solution. The reaction mixture was stirred for 3 h. This mixture poured onto water (5 mL) and extracted with CH₂Cl₂ (3 x 5 mL). Then washed by 1.0 M HCl (10 mL), aqueous NaHCO₃ (10 mL) and brine (10 mL). The organic phase was dried with anhydrous Na₂SO₄ and concentrated in vacuo to give brown oil. This oil was further purified by RP-HPLC using protocols described in the general method. Fractions were collected, concentrated and lyophilized to give Hoshinoamides A as a white solid (10 mg, 2% yield).

The ¹H NMR and ¹³C NMR spectra of synthetic product were fully consistent with the data of isolated samples reported in the literature. See table S2 and table S3 for details. ¹H NMR (400 MHz, Methanol-d₄) δ 7.30 – 7.11 (m, 6H), 7.02 – 6.94 (m, 2H), 6.72 – 6.65 (m, 2H), 5.73 (dd, J = 9.2, 6.4 Hz, 1H), 4.82 – 4.73 (m, 1H), 4.64 – 4.53 (m, 2H), 4.43 – 4.25 (m, 2H), 3.69 (s, 2H), 3.50 (dt, J = 11.2, 6.0 Hz, 1H), 3.41 – 3.31 (m, 1H), 3.20 – 3.06 (m, 9H), 2.99 – 2.92 (m, 3H), 2.91 – 2.86 (m, 1H), 2.52 (t, J = 7.6 Hz, 2H), 2.47 – 2.38 (m, 2H), 2.29 – 2.22 (m, 3H), 2.18 (q, J = 7.7 Hz, 3H), 2.05 – 1.99 (m, 1H), 1.99 – 1.71 (m, 9H), 1.68 – 1.46 (m, 6H), 1.46 – 1.34 (m, 4H), 1.11 – 0.97 (m, 3H), 0.97 – 0.81 (m, 16H), 0.68 – 0.55 (m, 6H). ¹³C NMR (101 MHz, MeOD) δ 177.43, 176.52, 176.00, 174.55, 173.86, 173.15, 173.09, 172.87, 171.89, 170.47, 156.60, 138.40, 133.75, 130.69, 130.40, 129.45, 127.70, 116.18, 64.21, 60.84, 57.23, 55.69, 55.64, 55.52, 54.32, 52.69, 49.68, 49.46, 49.25, 49.25, 49.04, 48.83, 48.81, 48.61, 48.40, 40.23, 38.43, 37.82, 36.62, 35.76, 35.51, 34.59, 32.62, 31.80, 31.59, 31.56, 30.22, 29.98, 29.20, 27.72, 26.21, 26.17, 26.06, 25.95, 25.90, 25.11, 23.80, 22.17, 20.39, 19.90, 19.49, 18.13, 16.50, 11.60. HRMS: (+ESI) Calc. for C₆₁H₉₅N₉O₁₂: 1146.7173 [M+H]+, Found: 1146.7173 [M+H]+

Supporting Information

Supporting Information File 1:
Acknowledgements

This research was supported by the Natural Science key Project of Anhui Education Department (Grant No. KJ2019A0635); Provincial University Students’ Innovation and Entrepreneurship Program (Grant No. 2019CXXL077); Hubei Province Key Laboratory of Occupational Hazard Identification and Control, Wuhan University of Science and Technology (Grant No. OHIC2020Y06)

References

[1] Cowman A. F., Healer J, Marapana D, Marsh K. Cell. 2016, 167(3), 610–624.
[2] WHO, World Health Organization, World malaria report 2020
[3] Singh, S. K.; Singh, S. Int. J. Pharm. Sci. Rev. Res. 2014, 25, 209–302.
[4] Achan, J.; Talisuna, A. O.; Erhart, A.; Yeka, A.; Tibenderana, J. K.; Baliraine, F. N.; Rosenthal, P. J.; D'Alessandro, U. Malaria J. 2011, 10, No. 144.
[5] Kumar S.; Bhardwaj T.; Prasad D.; Singh R. K.; Biomed Pharmacother. 2018, 104, 8-27.
[6] Golenser J.; Wakhne J. H.; Krugliak M.; Hunt N. H.; Grau G. E.; Int J Parasitol. 2006,36(14),1427-1441.
[7] Hsu, E. Trans. R. Soc. Trop. Med. Hyg. 2006, 100, 505–508.
[8] Devine, S. M.; Challis, M. P.; Kigotho, J. K.; Siddiqui, G.; Paoli, A. D.; MacRaild, C. A.; Avery, V. M.; Creek, D. J.; Norton, R. S.; Scammells P. J.; * Eur. J. Med. Chem. 2021, 221, 113518

[9] Shibeshi, M. A.; Kifle, Z. D.; Atnafie, S. A.; * Infection and Drug Resistance 2020:13 4047–4060

[10] Ojha, P. K.; Kumar, V.; Roy, J.; Roy, K.; Expert Opinion on Drug Discovery 2021, 16(6), 659-695.

[11] Iwasaki, A.; Tadenuma, T.; Sumimoto, S.; Shiota, I.; Matsubara, T.; Saito-Nakano, Y.; Nozaki, T.; Sato, T.; Suenaga, K. J. Nat. Prod. 2018, 81, 2545–2552.

[12] Iwasaki, A.; Ohtomo, K.; Kurisawa, N.; Shiota, I.; Rahmawati, Y.; Jeelani, G.; Nozaki, T.; Suenaga, K. J. Nat. Prod. 2021, 84, 126-135.