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ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · SEPTEMBER 2014

Impact Factor: 3.45 · DOI: 10.1016/j.ejmech.2014.09.077

European Journal of Medicinal Chemistry 87 (2014) 364–371

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Diastereoselective synthesis of potent antimalarial cis-β-lactam agents through a [2 + 2] cycloaddition of chiral imines with a chiral ketene

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ARTICLE INFO

Article history:
Received 7 June 2014
Received in revised form
21 September 2014
Accepted 24 September 2014
Available online 28 September 2014

Keywords:
β-lactam
Chiral imine
Chiral ketene
Staudinger reaction
Diastereoselective
Antimalarial activity

ABSTRACT

The effect of double asymmetric induction for the synthesis of new cis-β-lactams by [2 + 2] cycloaddition reactions of chiral imines with a chiral ketene was investigated. The cycloaddition reaction was found to be totally diastereoselective leading exclusively to the formation of the *cis*-β-lactam derivatives. The newly synthesized cycloadducts were evaluated for their antimalarial activities against *Plasmodium falciparum* K14 resistant strain with moderate to excellent IC_{50} values varying from 8 to 50 μM. Of the fifteen β-lactams tested, four showed $IC_{50} \leq 11$ μM.

1. Introduction

The β-lactam skeleton is the key structural unit responsible for the antibacterial property of the most widely employed antibacterial agents [1]. 2-Azetidinones demonstrate numerous other interesting biological properties, such as cholesterol absorption inhibitors [2], human cytomegalovirus (HCMV) protease inhibitors [3], thrombin inhibitors [4], antihyperglycemic [5], antitumor [6], anti-HIV [7], anti inflammatory, analgesic activities [8], antimalarial activities [9], antifungal [10], antiproliferative activities [11], antitubercular [12], anti-oxidant [13], insecticidal activities [14] and serine-dependent enzyme inhibitors [15]. As a consequence, a large number of synthetic methods for β-lactams are now available, and the topic has been reviewed on more than one occasion [16]. The most convenient procedure for the synthesis of the β-lactam ring skeleton is the [2 + 2] cyclocondensation of ketenes to the imines, known as the Staudinger reaction [17]. In particular, this method has provided useful and economical entries to β-lactams, mainly due to the availability of both Schiff's bases and ketenes. In this context, in spite of the high level of achievement reached in the Staudinger reaction, the subject still continues to be an active area of research [18]. Over the past few years, asymmetric versions of this reaction has been extensively developed using a combination of either chiral ketenes and a chiral imines or a chiral ketenes and chiral imines, generally providing good diastereoselectivity [19]. In these cases, chiral starting materials such as aldehydes, acids/acid halides and amines have been widely used. High levels of stereoselection have been achieved when the β-carbon of the chiral aldehyde is attached to a hetero-atom [20]. Recently, several researchers have studied different approaches to obtain β-lactams [21–23] with moderate to excellent diasteromeric excesses including the reaction of an acid derived from menthol and a Schiff base derived from an optically active amine. Also, some catalytic asymmetric synthesis of β-lactam by [2 + 2] cycloaddition reaction has been reported [24,25]. In this context we will report herein our results dealing with the diastereoselective synthesis of potent antimalarial *cis*-β-lactam agents through a [2 + 2] cycloaddition of chiral imines with a chiral ketene.

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http://dx.doi.org/10.1016/j.ejmech.2014.09.077
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2. Results and discussion

Mono asymmetric induction was checked by using the chiral ketene derived from (−)-menthol **1**. In this context, menthoxyacetic acid (2-(((1R,2S,5R)-2-isopropyl-5- methylcyclohexyl)oxy)acetic acid) [26] **2** was prepared by refluxing a mixture of chloroacetic acid and (−)-menthol in the presence of Na in toluene (Scheme 1).

Subsequent reaction of menthoxyacetic acid **2** in the presence of triethylamine, tosyl chloride and Schiff base **3** afforded *cis*-β-lactams **4** and **5** by ratio 60/40 (Scheme 2) in 50% isolated yield. Performing this reaction at −78 °C did not lead to a significant improvement of both chemical yield and diastereoselectivity. The *cis* and *trans* stereochemistries of 2-azetidinones were deduced from the coupling constants of H-3 and H-4 ($J_{3,4} > 4.0$ Hz for the cis and $J_{3,4} < 3.0$ Hz for the trans stereoisomer) [19,27].

Fig. 1 showed the ^{1}H NMR spectra of *cis*-β-lactams **4** and **5** mixture. In part **A**, four doublets for H-3 and H-4 of β-lactam ring were encountered and the extended peaks of these doublets are presented in part **B**. H-3 of one resonated at 5.13 ppm ($J = 5.04$ Hz) whereas H-3 of the other ring resonated at 5.10 ppm ($J = 4.9$ Hz).

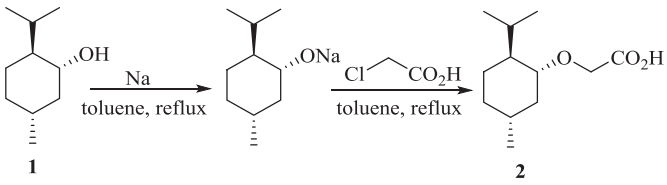
On the basis of this disappointing result, another way for the obtaining of diastereomerically pure *cis*-β-lactams had been envisioned. Thus, treatment of (*S*)-(−)-1-phenylethanamine [28] with substituted benzaldehydes in refluxing ethanol afforded the chiral imines **6a**–**m**. [29–36] As a model reaction, Schiff base **6a** was treated with phenoxyacetic acid in the presence of triethylamine and tosyl chloride to afford *cis*-β-lactams **7**and **8** (Scheme 3).

Nevertheless, once again the expected products were obtained as a mixture of the two diastereomers in a 55/45 diastereomic ratio. This was unambiguously confirmed by ^{1}H NMR analysis for which β-lactams **7** and **8** present similarly four doublets for H-3 and H-4 of β-lactam ring (Fig. 2).

Finally, we envisioned performing a double asymmetric induction for the synthesis of new *cis*-β-lactams involving a [2 + 2] cycloaddition reaction of various chiral imines in the presence of a chiral ketene (Scheme 4). Thus, the reaction of chiral imines **6a**–**m** with chiral menthoxyacetic acid in the presence of triethylamine and tosyl chloride afforded *cis*-β-lactams **9a**–**m** in a pure diastereomerically form (Table 1).

Unfortunately, *cis*-β-lactams **9a**–**m** were not suitable for crystallographic studies but all the cycloadducts were fully characterized by spectral and elemental analyses. Typically, for compound **9a** the ^{1}H NMR spectrum exhibited the β-lactam ring hydrogen H-4 as a doublet at 4.41 ppm ($J = 4.9$ Hz) and H-3 as a doublet at 4.68 ppm ($J = 4.9$ Hz). No others signal corresponding to the other diastereomer is encountered demonstrating the efficiency and selectivity of this methodology (Fig. 3).

The relative stereochemistry of **9a** was deduced using NOE experiment as shown in Fig. 4. Irradiation of hydrogen H-b (H-4) resulted in an enhancement of H-c (7.1%) and also H-a (H-3) changed to a singlet. It should be mentioned that, irradiation of hydrogen H-a (H-3) was shown same result with interaction between H-b (H-4), but not observed interaction between the H-d. So, The NOE experiment was suggested that the H-a and H-b were oriented to the opposite side of the β-lactam plane.



Scheme 1. Synthesis of menthoxyacetic acid **2**.

All of these newly synthesized β-lactams derivatives were subsequently evaluated for their biological activities. Firstly, it has been demonstrated that these compounds do not possess significant antimicrobial activities against Gram-positive *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli* or *Pseudomonas Aeruginosa*. Nevertheless, moderate to excellent antimalarial activities have been obtained against chloroquine resistant *Plasmodium falciparum* K14 strain as outlined in Table 2 with IC_{50} varying from 8 to up to 50 μM. On the other hand, a strong influence of the substituents beared on the phenyl group of the considered lactam derivative is noticed even if the mechanism of action remains unclear to date [9].

SAR study of β-lactams in present study suggests that the methoxy substituents on the phenyl group on C-4 of β-lactam ring (**9d**, **9e**, and **9f**) were required for good antimalarial activity. Compound **9j** having the 4-bromophenyl group showed the same activity as the reference chloroquine. The naphthyl group on the C-4 of the β-lactam ring (**9m**) exhibited the better activity than chloroquine.

3. Conclusion

This article describes for the first time the synthesis and characterization of some examples of mono and double asymmetric *cis*-β-lactams. The effect of a double asymmetric induction for the synthesis of new *cis*-β-lactams by [2 + 2] cycloaddition reactions of chiral imines with a chiral ketene was successfully investigated leading to the expected products in a diastereselective pure form. Otherwise, these derivatives demonstrate moderate to excellent IC_{50} values varying from 8 to up to 50 μM against *P. falciparum* K14 resistant strain.

4. Experimental section

4.1. General

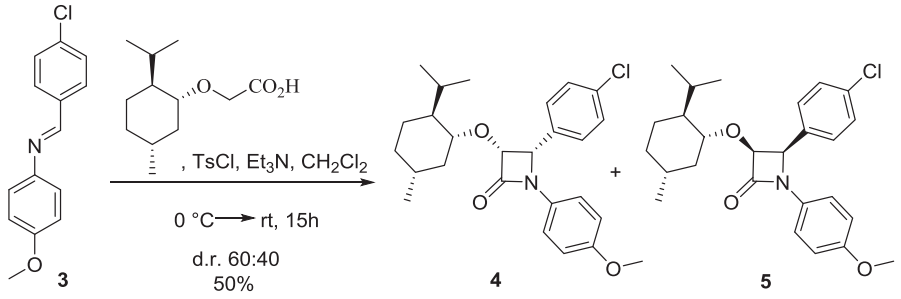
All needed chemicals were purchased from Merck, Fluka and Acros chemical companies. All reagents and solvents were dried prior to use according to standard methods [37]. IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using a Bruker Avance DPX instrument (^{1}H NMR 250 MHz, ^{13}C NMR 62.9 MHz). Chemical shifts were reported in parts per million (δ) downfield from TMS. All of the coupling constants (J) are in hertz. Optical rotations were measured on a Perkin Elmer 241 Polarimeter at 25 °C in chloroform. The mass spectra were recorded on a Shimadzu GC–MS QP 1000 EX instrument. Elemental analyses were run on a Thermo Finnigan Flash EA-1112 series. Melting points were determined in open capillaries with Buchi 510 melting point apparatus. Thin-layer chromatography was carried out on silica gel F254 analytical sheets obtained from Fluka. Column chromatography was performed on Merck Kieselgel (230–270 mesh).

4.2. General procedure for preparation Schiff bases by chiral amine

A mixture of (*S*)-1-phenylethanamine (1.00 mmol) and different aldehyde (1.00 mmol) was refluxed in ethanol (20 ml) for several hours. Evaporation of the solvent afforded the crude imines either as oil or solid, which were used for the next step without further purification. Some of these Schiff bases were purified by crystallization from ethanol and characterized.

4.2.1. (S)–N-(4-Chlorobenzylidene)-1-phenylethana mine (*6a*)

White crystals in 75% yield; Mp. 72–74 °C; $[\alpha]_D^{25} = +91.68$ (*c* 0.021, $CHCl_3$); IR (KBr, cm^{-1}): 1639 (C=N); ^{1}H NMR (250 MHz,



Scheme 2. Synthesis of *cis*-β-lactams **4** and **5**.

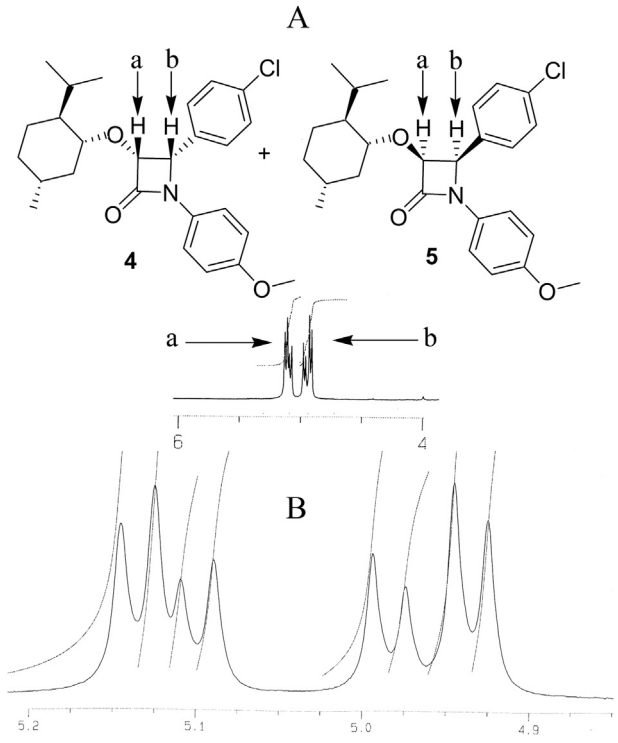
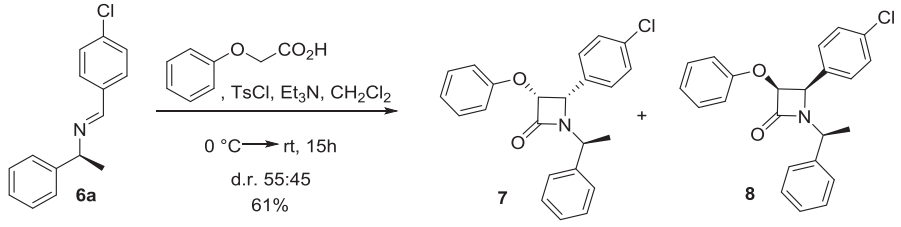


Fig. 1. ^{1}H NMR spectra of H-3 and H-4 of the β-lactams 4 and 5 A) Ordinary spectrum; B) Expanded spectrum.



Scheme 3. Synthesis of *cis*-β-lactams **7** and **8**.

$CDCl_3$) δ 8.28 (CHN, s, 1H), 7.69 (ArH d, 2H, $J = 8.5$), 6.99–7.42 (ArH, m, 7H), 4.51 (N–CHMe, q, 1H, $J = 6.6$) 1.57 (N–CHMe, d, 3H, $J = 6.6$); Analysis calculated for $C_{15}H_{14}ClN$: C, 73.92; H, 5.79; N, 5.75%. Found: C, 73.95; H, 5.82; N, 5.78%.

*4.2.2. (S)–N-(3,4-Dimethoxybenzylidene)-1-phenyle thanamine (**6f**)*

White crystals in 61% yield; Mp. 76–78 °C; $[\alpha]_D^{25} = +97.16$ (*c* 0.015, $CHCl_3$); IR (KBr, cm^{-1}): 1638 (C=N); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.55 (CHN, s, 1H), 7.12–7.48 (ArH, m, 7H) 6.81 (ArH d, 1H, $J = 7.9$), 4.48 (N–CHMe, q, 1H, $J = 6.6$), 3.83, 3.93 (2OMe, s, 6H), 1.83 (N–CHMe, d, 3H, $J = 6.6$), Analysis calculated for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20%. Found: C, 75.83; H, 7.15; N, 5.24%.

*4.2.3. (S)–N-(4-Methylbenzylidene)-1-phenylethana mine (**6g**)*

Yellow solid 90% yield, Mp. 82–84 °C, $[\alpha]_D^{25} = +97.48$ (*c* 0.018, $CHCl_3$), IR (KBr, cm^{-1}): 1648 (C=N), ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.98 (CHN, s, 1H), 7.64 (ArH d, 2H, $J = 8.1$), 7.11–7.39 (ArH, m, 7H), 4.45 (N–CHMe, q, 1H, $J = 6.6$), 2.29 (Me, s, 3H), 1.53 (N–CHMe, d, 3H, $J = 6.6$); Analysis calculated for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27%. Found: C, 86.11; H, 7.63; N, 6.31%.

*4.2.4. (S)–N-(4-Bromobenzylidene)-1-phenylethana mine (**6j**)*

White solid 83% yield; Mp. 78–80 °C; $[\alpha]_D^{25} = +80.38$ (*c* 0.031, $CHCl_3$); IR (KBr, cm^{-1}): 1638 (C=N); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.57 (CHN, s, 1H), 7.62 (ArH d, 1H, $J = 8.37$), 7.49 (ArH d, 1H, $J = 8.4$), 6.90–7.42 (ArH, m, 7H), 4.51 (N–CHMe, q, 1H, $J = 6.6$), 1.58 (N–CHMe, d, 3H, $J = 6.6$); Analysis calculated for $C_{15}H_{14}BrN$: C, 62.52; H, 4.90; N, 4.86%. Found: C, 62.56; H, 4.94; N, 4.81%.

*4.2.5. (S)–N-(2-Nitrobenzylidene)-1-phenylethanami ne (**6l**)*

Light yellow crystals in 73% yield; Mp. 44–46 °C; $[\alpha]_D^{25} = +57.83$ (*c* 0.013, $CHCl_3$); IR (KBr, cm^{-1}): 1633 (C=N); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.59 (ArH s, 1H), 8.41 (CHN, s, 1H), 8.09 (ArH d, 2H, $J = 7.7$), 7.25–758 (ArH, m, 6H), 4.59 (N–CHMe, q, 1H, $J = 6.6$), 1.57 (N–CHMe, d, 3H, $J = 6.6$); Analysis calculated for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02%. Found: C, 70.81; H, 5.57; N, 11.08%.

*4.2.6. (S)–N-(Naphthalen-2-ylmethylene)-1-phenylet hanamine (**6m**)*

White solid 93% yield; Mp. 136–138 °C; $[\alpha]_D^{25} = +30.78$ (*c* 0.014, $CHCl_3$); IR (KBr, cm^{-1}): 1628 (C=N); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.49 (CHN, s, 1H), 8.02–8.08 (ArH, m, 2H), 7.80–7.86 (ArH, m, 4H), 7.13–7.49 (ArH, m, 6H), 4.59 (N–CHMe, q, 1H, $J = 6.6$), 1.59 (N–CHMe, d, 3H, $J = 6.6$); Analysis calculated for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40%. Found: C, 88.03; H, 6.66; N, 5.43%.

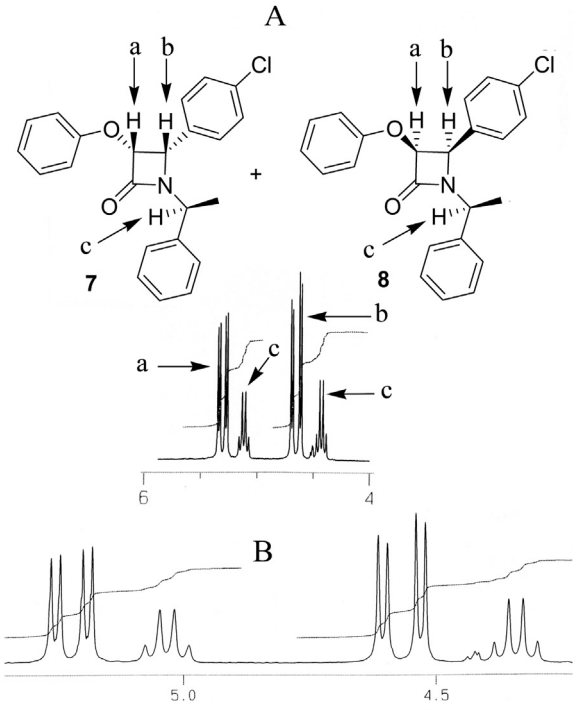
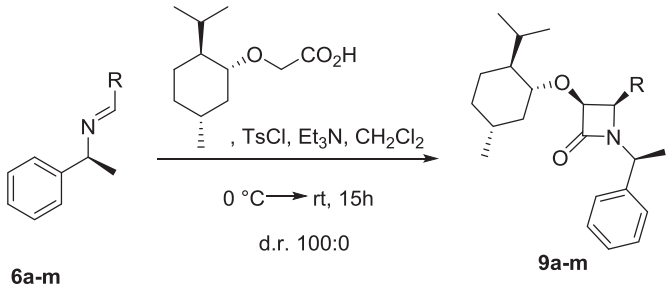


Fig. 2. ^{1}H NMR spectra of H-3 and H-4 of the β-lactams **7** and **8** A) Ordinary spectrum; B) Expanded spectrum.



Scheme 4. Synthesis of *cis*-β-lactams **9a**–**m**.

4.3. General procedure for the synthesis of asymmetric β-lactams

A mixture of Schiff base (1.00 mmol), triethylamine (5.00 mmol), 2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy) acetic acid (1.50 mmol) and tosyl chloride (1.50 mmol) in dry CH_2Cl_2 (15 mL) was stirred at 0 °C to room temperature for 24 h. Then it was washed with HCl 1N (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated to give the product either as a solid or an oil, which was then purified by recrystallization from ethanol or EtOAc or column chromatography, EtOAc/petroleum ether (9/1 to 8/2) as the eluent solvent.

4.3.1. 4-(4-chlorophenyl)-3-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-1-(4-meth oxyphenyl)azetidin-2-one (**4.5**)

Recrystallization from EtOAc. White solid (Yield 50%); Mp: 176–178 °C; $[\alpha]_D^{25} = +54.7$ (*c* 0.100, $CHCl_3$); IR (KBr, cm^{-1}): 1741 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ in mixcure of two diastereomer 6.75–8.27 (ArH, m, 6H) 6.77 (ArH d, 2H, $J = 7.8$), one diastereomer 5.10 (H-3, d, 1H, $J = 4.9$), 4.98 (H-4, d, 1H, $J = 4.9$), another diastereomer 5.13 (H-3, d, 1-H, $J = 5$), 4.93 (H-4, d, 1-H, $J = 5$), 3.72 (OMe, s, 3H), 3.02 (CH–O menthoxy, m, 1H), 0.32–2.20 (H menthoxy, m, 18H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 165.1 (CO β-lactam), 156.2, 134.2, 132.9, 130.5, 129.3, 128.4, 118.6, 114.3 (aromatic carbons), 82.3 (C-3), 81.1 (CH–O, menthoxy), 62.0 (C-4), 55.3 (OMe), 47.4, 40.9, 34.1, 31.3, 24.9, 23.1, 22.2, 20.7, 15.9 (menthoxy carbons); GC–MS $m/z = 444$ [M^+, ^{37}Cl], 442 [M^+, ^{35}Cl]; Analysis calculated for $C_{26}H_{32}ClNO_3$: C, 70.65; H, 7.30; N, 3.17%. Found: C, 70.67; H, 7.35; N, 3.21%.

4.3.2. 4-(4-Chlorophenyl)-3-phenoxy-1-((S)-1-phenylethyl) azetidin-2-one (**7.8**)

Recrystallization from EtOAc. White solid (Yield 61%); Mp: 118.120 °C; $[\alpha]_D^{25} = +5.66$ (*c* 0.001, $CHCl_3$); IR (KBr, cm^{-1}): 1734 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$): δ in mixcure of two diastereomer 7.01–7.24 (ArH, m, 12H), 6.75–6.84 (ArH, m, 1H), 6.51–6.67 (ArH, m, 1H), one diastereomer 5.25 (H-3, d, 1H, $J = 4.5$), 4.60 (H-4, d, 1H, $J = 4.5$), another diastereomer 5.18 (H-3, d, 1H, $J = 4.6$), 4.52 (H-4, d, 1H, $J = 4.6$), 5.04 and 4.31 [N–CHMe, q, 1H, $J = 7.1$], 1.75 and 1.28 (N–CHMe, d, 3H, $J = 7.1$); ^{13}C NMR (62 MHz, $CDCl_3$) δ 165.4 (CO β-lactam), 156.7, 139.1, 130.1, 129.2, 128.8, 128.3, 128.1, 127.9, 126.9, 122.1, 114.8 (aromatic carbons), 81.03 (C-3), 67.3 (C-4), 52.3, 54.3 (CH), 19.1, 19.6 (Me); GC–MS $m/z = 442$ [M^+, ^{37}Cl], 440 [M^+, ^{35}Cl]; Analysis calculated for $C_{23}H_{20}ClNO_2$: C, 73.11; H, 5.33; N, 3.71%. Found: C, 73.20; H, 5.45; N, 3.65%.

4.3.3. 4-(4-chlorophenyl)-3-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)-1-((S)-1-phenylethyl)azetidin-2-one (**9a**)

Recrystallization from EtOAc. White solid (Yield 35%); Mp: 128–130 °C; $[\alpha]_D^{25} = +27.95$ (*c* 0.020, $CHCl_3$); IR (KBr, cm^{-1}): 1743 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.22–7.36 (ArH, m, 5H), 7.19–7.21(ArH, m, 4H), 5.07 (N–CHMe, q, 1H, $J = 7.1$), 4.68 (H-3, d, 1H, $J = 4.9$), 4.21 (H-4, d, 1H, $J = 4.9$), 2.85 (CH–O, menthoxy), 0.32–2.20 (H menthoxy and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.4 (CO β-lactam), 139.5, 134.7, 133.9, 130.1, 128.6, 128.3, 127.8, 127.1(aromatic carbons), 82.1 (C-3), 80.6 (CH–O, menthoxy), 61.1 (C-4), 51.7 (N–CHMe), 47.4, 40.9, 34.1, 31.3, 24.7, 22.8, 22.1, 20.9, 19.0, 15.6 (menthoxy carbons and N–CHMe); GC–MS $m/z = 442$ [M^+, ^{37}Cl], 440 [M^+, ^{35}Cl]; Analysis calculated for $C_{27}H_{34}ClNO_2$: C, 73.70; H, 7.79; N, 3.18%. Found: C, 73.75; H, 7.74; N, 3.23%.

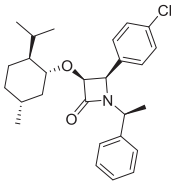
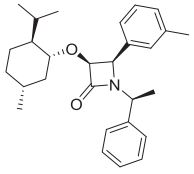
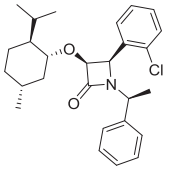
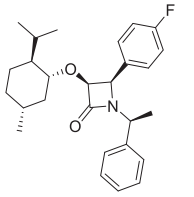
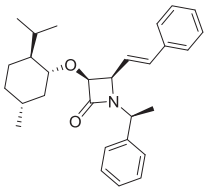
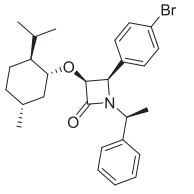
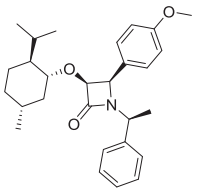
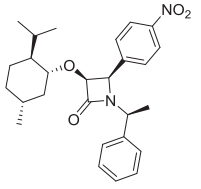
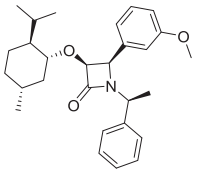
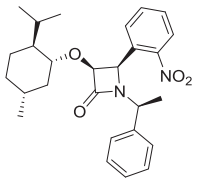
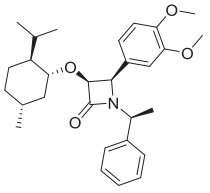
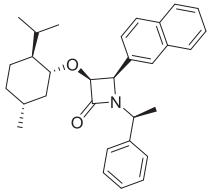
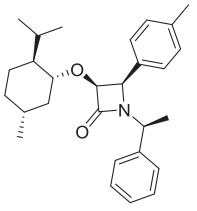
4.3.4. 4-(2-Chlorophenyl)-3-((1R,2S,5R)-2-isopropyl-5-methyclcyclohexyloxy)-1-((S)-1-phenylethyl)azetidin-2-one (**9b**)

Yellow oil (Yield 32%); $[\alpha]_D^{25} = +29.36$ (*c* 0.017, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1747 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.21 (ArH d, 1H, $J = 8.7$), 6.93–7.06 (ArH, m, 8H), 4.85 (H-3, d, 1H, $J = 5$), 4.73 (N–CHMe, q, 1H, $J = 7.1$], 4.48 (H-4, d, 1H, $J = 5$), 2.65 (CH–O, menthoxy), 0.02–1.82 (H menthoxy and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.8 (CO β-lactam); 139.8, 133.5, 129.1, 128.8, 128.5, 127.6, 126.8, 126.1 (aromatic carbons), 81.9 (C-3), 80.7 (CH–O, menthoxy), 58.3 (C-4), 52.5 (N–CHMe), 47.5, 40.9, 34.1, 31.4, 24.5, 23.1, 22.0, 20.8, 19.3, 15.7 (menthoxy carbons and N–CHMe); GC–MS $m/z = 442$ [M^+, ^{37}Cl], 440 [M^+, ^{35}Cl]; Analysis calculated for $C_{27}H_{34}ClNO_2$: C, 73.70; H, 7.79; N, 3.18%. Found: C, 73.79; H, 7.73; N, 3.14%.

4.3.5. 3-((1R,2S,5R)-2-isopropyl-5methylcyclohexyloxy)-1-((S)-1-phenylethyl)-4-((E)-styryl)azetidin-2-one (**9c**)

Recrystallization from ethanol. White solid (Yield 55%); Mp: 104–106 °C; $[\alpha]_D^{25} = +10.09$ (*c* 0.011, $CHCl_3$); IR (KBr, cm^{-1}): 1743 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24–7.35 (ArH, m, 10H), 6.45 (CH-Ph, d, 1H, $J = 15.9$), 6.28 (C-3-CH, dd, 1H, $J = 9.1$, $J = 15.9$), 5.03 (N–CHMe, q, 1H, $J = 7.1$), 4.65 (H-3, d, 1H, $J = 4.8$), 4.10 (H-4, dd, 1H, $J = 4.8$, $J = 9.1$), 2.15 (CH–O, menthoxy), 0.18–2.00 (H menthoxy and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 167.5 (CO β-lactam), 139.7, 139.3, 134.3, 128.6, 128.1, 127.7, 127.3, 126.6, 126.5,

Table 1
Isolated yields for *cis*-β-lactams derivatives **9a**–**m**.

β-lactam	Structure	Yield (%)[a] (d.r. (%))	β-lactam	Structure	Yield (%)[a] (d.r. (%))
9a		35 (100:0)	**9h**		34 (100:0)
9b		32 (100:0)	**9i**		30 (100:0)
9c		55 (100:0)	**9j**		33 (100:0)
9d		60 (100:0)	**9k**		37 (100:0)
9e		50 (100:0)	**9l**		43 (100:0)
9f		51 (100:0)	**9m**		40 (100:0)
9g		27 (100:0)			

[a] Isolated yields of pure products.

(aromatic carbons and alkenes carbons), 82.6 (C-3), 81.2 (CH–O, menthoxy), 60.9 (C-4), 51.3 (N–CHMe), 47.4, 41.1, 34.1, 31.4, 24.8, 22.8, 22.2, 20.7, 19.2, 15.5 (menthoxy carbons and N–CHMe); GC–MS m/z = 431 [M^+]; Analysis calculated for $C_{29}H_{37}NO_2$: C, 80.70; H, 8.64; N, 3.25%. Found: C, 80.75; H, 8.60; N, 3.29%.

*4.3.6. 3-((1R,2S,5R)-2-isopropyl-5methylcyclohexyloxy)-4-(4-methoxyphenyl)-1-((S)-phenylethyl)azetidin-2-one (**9d**)*

Recrystallization from EtOAc. White solid (Yield 60%); Mp: 96–98 °C; $[\alpha]_D^{25}$ = +19.24 (*c* 0.024, $CHCl_3$); IR (KBr, cm^{-1}): 1737 (CO β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 7.18–7.32 (ArH, m, 7H), 6.64

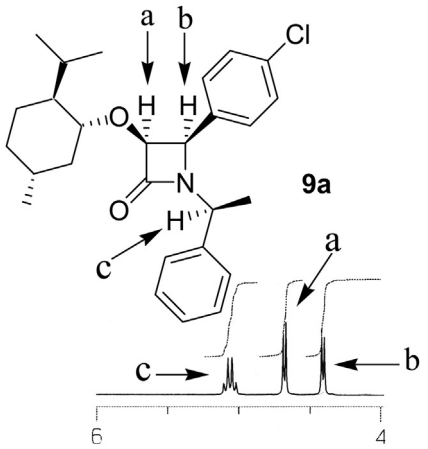


Fig. 3. ^{1}H NMR spectrum of single diastereomer of β-lactam **9a**.

(ArH d, 2H, J = 8.8), 5.08 (N–CHMe, q, 1H, J = 7.1), 4.66 (H-3, d, 1H, J = 4.8), 4.40 (H-4, d, 1H, J = 4.8), 3.81 (OMe, s, 3H), 2.85 (CH–O, menthoxy), 0.16–2.11 (H menthoxy and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.6 (CO β-lactam), 159.7, 139.7, 129.9, 128.6, 128.2, 127.7, 127.2, 113.3 (aromatic carbons), 82.0 (C-3), 80.5 (CH–O, menthoxy), 61.1 (C-4), 55.2 (OMe), 51.4 (N–CHMe), 47.4, 40.9, 34.1, 31.4, 24.8, 22.6, 22.2, 20.7, 19.0, 15.6, (menthoxy carbons and N–CHMe); GC–MS m/z = 435 [M^+]; Analysis calculated for $C_{28}H_{37}NO_3$: C, 77.20; H, 8.56; N, 3.22%. Found: C, 77.26; H, 8.61; N, 3.28%.

4.3.7. 3-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-4-(3-methoxyphenyl)-1-((S)-1-phenylethyl)azetidin-2-one (**9e**)

Light yellow oil (Yield 50%); $[\alpha]_D^{25}$ = −39.72 (c 0.090, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1755 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.99–7.09 (ArH, m, 5H). 6.63–6.65 (ArH, m, 4H), 5.08 (N–CHMe, q, 1H, J = 7.1), 4.66 (H-3, d, 1H, J = 4.7), 4.40 (H-4, d, 1H, J = 4.7), 3.81 (OMe, s, 3H), 2.85 (CH–O, menthoxy), 0.16–2.11 (H menthoxy and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.6 (CO β-lactam), 159.4, 141.3, 137.7, 128.8, 127.2, 121.2, 113.3 (aromatic carbons), 82.6 (C-3), 80.6 (CH–O, menthoxy), 62.1 (C-4), 54.9 (OMe), 53.9 (N–CHMe),47.4, 40.9, 34.1, 31.4, 24.6, 22.5, 22.3, 20.8, 19.7, 16.3 (menthoxy carbons and N–CHMe); GC–MS m/z = 435 [M^+]; Analysis calculated for $C_{28}H_{37}NO_3$: C, 77.20; H, 8.56; N, 3.22%. Found: C, 77.24; H, 8.51; N, 3.18%.

4.3.8. 4-(3,4-Dimethoxyphenyl)-3-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-1-((S)-1-phenylethyl)azetidin-2-one (9f)

Light yellow oil (Yield 51%); $[\alpha]_D^{25}$ = −33.30 (c 0.038, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1736 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$)

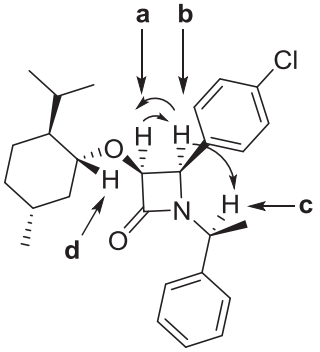


Fig. 4. Key NOE correlations for **9a**.

Table 2
Antimalarial activities of *cis*-β-lactams **5**, **6**, **7**, **8** and **9a**–**m** against chloroquine resistant *Plasmodium falciparum* K14 strain.

Product	IC_{50} (μM)	Product	IC_{50} (μM)
Chloroquine	11	**9f**	8
4,5	>50	**9g**	35
7,8	42	**9h**	42
9a	33	**9i**	19
9b	36	**9j**	11
9c	>50	**9k**	27
9d	13	**9l**	21
9e	8	**9m**	10

δ 7.19–7.31 (ArH, m, 5H), 6.76–6.80 (ArH, m, 3H), 5.09 (N–CHMe, q, 1H, J = 7.1), 4.78 (H-3, d, 1H, J = 4.8), 4.72 (H-4, d, 1H, J = 4.8), 3.71, 3.78 (2OMe, s, 6H), 2.83 (CH–O, menthoxy), 0.16–2.21 (H menthoxy and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.3 (CO β-lactam), 148.9, 148.3, 141.0.140.0, 128.4, 128.1, 127.3, 127.0, 121.1, 111.6, 110.2 (aromatic carbons), 82.3 (C-3), 80.6 (CH–O, menthoxy), 61.9 (C-4), 55.3, 55.6 (2OMe), 52.0 (N–CHMe), 47.8, 40.7, 34.1, 31.4, 24.8, 22.7, 22.6, 20.6, 19.1, 16.1 (menthoxy carbons and N–CHMe), GC–MS m/z = 465 [M^+]; Analysis calculated for $C_{29}H_{39}NO_4$: C, 74.81; H, 8.44; N, 3.01%. Found: C, 74.86; H, 8.49; N, 3.12%.

4.3.9. 3-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-1-((S)-1-phenylethyl)-4-p-tolylazetidin-2-one (**9g**)

Recrystallization from ethanol. White solid (Yield 27%); Mp: 82–84 °C; $[\alpha]_D^{25}$ = −18.27 (c 0.003, $CHCl_3$); IR (KBr, cm^{-1}): 1741 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.08–7.36 (ArH, m, 9H), 5.09 (N–CHMe, q, 1H, J = 7.1], 4.67 (H-3, d, 1H, J = 4.8), 4.41 (H-4, d, 1H, J = 4.8), 2.82 (CH–O, menthoxy), 2.34 (Me, s, 3H), 0.12–2.10 (H menthoxy, and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.7 (CO β-lactam), 139.7, 137.8, 132.9, 128.6, 127.7, 127.5, 127.0, 126.7 (aromatic carbons), 82.0 (C-3), 80.5 (CH–O, menthoxy), 61.6 (C-4), 51.5 (N–CHMe), 47.9, 40.8, 34.2, 31.3, 24.5, 22.8, 22.2, 21.1, 20.8, 19.0, 15.6 (menthoxy carbons, Me and N–CHMe); GC–MS m/z = 419 [M^+]; Analysis calculated for $C_{28}H_{37}NO_2$: C, 80.15; H, 8.89; N, 3.34%. Found: C, 80.11; H, 8.83; N, 3.38%.

4.3.10. 3-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-1-((S)-1-phenylethyl)-4-m-tolylazetidin-2-one (**9h**)

Light yellow oil (Yield 34%); $[\alpha]_D^{25}$ = +41.21 (c 0.038, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1755 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.77–7.23 (ArH, m, 9H); 4.81 (N–CHMe, q, 1H, J = 7.1], 4.57 (H-3, d, 1H, J = 4.8), 4.46 (H-4, d, 1H, J = 4.5), 3.14 (CH–O, menthoxy), 2.08 (Me, s, 3H), 0.38–2.05 (H menthoxy, and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.4 (CO β-lactam); 141.1, 139.9, 137.0, 135.8, 134.6, 129.6, 128.7128.4, 127.6127.1, 125.8 (aromatic carbons), 82.2 (C-3), 80.3 (CH–O, menthoxy), 61.9 (C-4), 53.8 (N–CHMe), 47.9, 40.8, 34.2, 31.3, 24.5, 23.0, 22.1, 21.1.20.7 19.0.16.1 (menthoxy carbons, Me and N–CHMe), GC–MS m/z = 419 [M^+]; Analysis calculated for $C_{28}H_{37}NO_2$: C, 80.15; H, 8.89; N, 3.34%. Found: C, 80.20; H, 8.70; N, 3.28%.

4.3.11. 4-(4-Fluorophenyl)-3-((1R,2S,5R)-2isopropyl-5-methylcyclohexyloxy)-1-((S)-1-phenylethyl)azetidin-2-one (**9i**)

Recrystallization from EtOAc. White solid (Yield 30%); Mp: 116–118 °C; $[\alpha]_D^{25}$ = +6.14 (c 0.027, $CHCl_3$); IR (KBr, cm^{-1}): 1743 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.99–7.12 (ArH, m, 7H), 6.79 (ArH t, 2H, J = 8.6), 4.87 (N–CHMe, q, 1H, J = 7.1), 4.49 (H-3, d, 1H, J = 4.8), 4.26 (H-4, d, 1H, J = 4.8), 2.67 (CH–O, menthoxy), 0.02–1.34 (H menthoxy, and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.5 (CO β-lactam), 164.7, 160.8, 139.6, 131.8, 130.5, 128.6, 127.2, 114.6 (aromatic carbons), 82.2 (C-3), 80.9 (CH–O, menthoxy), 61.1

(C-4), 51.7 (N–CHMe), 15.6, 19.0, 20.6, 22.1, 22.9, 24.8, 31.4, 34.1, 41.0, 47.5 (menthoxy carbons and N–CHMe); GC–MS m/z = 423 [M^+]; Analysis calculated for $C_{27}H_{34}FNO_2$: C, 76.56; H, 8.09; N, 3.31%. Found: C, 76.51; H, 8.12; N, 3.27%.

4.3.12. 4-(4-Bromophenyl)-3-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-1-((S)-1-phenylethyl)azetidin-2-one (**9j**)

Recrystallization from ethanol. White solid (Yield 33%); Mp: 122.124 °C; $[\alpha]_D^{25}$ = +31.52 (*c* 0.016, $CHCl_3$); IR (KBr, cm^{-1}): 1743 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 (ArH d, 2H, *J* = 8.3), 7.21–7.34 (ArH, m, 2H), 7.13–7.20 (ArH, m, 5H), 5.08 (N–CHMe, q, 1H, *J* = 7.1), 4.48 (H-3, d, 1H, *J* = 4.8), 4.40 (H-4, d, 1H, *J* = 4.8), 2.84 (CH–O, menthoxy), 0.17–2.10 (H menthoxy, and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.4 (CO β-lactam), 139.4, 135.2, 131.0, 130.4, 128.6, 127.8127.2, 122.1 (aromatic carbons), 82.0 (C-3), 80.8 (CH–O, menthoxy), 61.2 (C-4), 51.7 (N–CHMe), 47.4, 40.9, 34.1, 31.4, 24.8, 22.9, 22.1.20.6.19.0, 15.6 (menthoxy carbons and N–CHMe), GC–MS m/z = 485 [M^+, ^{81}Br], 483 [M^+, ^{79}Br]; Analysis calculated for $C_{27}H_{34}BrNO_2$: C, 66.94; H, 7.07; N, 2.89%. Found: C, 66.98; H, 7.12; N, 2.95%.

4.3.13. 3-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-4-(4-nitrophenyl)-1-((S)-1-phenylethyl)azetidin-2-one (**9k**)

Recrystallization from ethanol. White solid (Yield 37%); Mp: 146–148 °C; $[\alpha]_D^{25}$ = +49.58 (*c* 0.041, $CHCl_3$); IR (KBr, cm^{-1}): 1741 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.16 (ArH d, 2H, *J* = 8.8), 7.45 (ArH d, 2H, *J* = 8.8), 7.19–7.33 (ArH, m, 5H), 5.04 (N–CHMe, q, 1H, *J* = 7.1), 4.78 (H-3, d, 1H, *J* = 5), 4.21 (H-4, d, 1H, *J* = 5), 2.91 (CH–O, menthoxy), 0.18–2.13 (H menthoxy, and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.2 (CO β-lactam), 147.7, 144.1, 139.3, 129.6, 128.4, 128.0, 127.1, 122.9 (aromatic carbons), 82.6 (C-3), 81.3 (CH–O, menthoxy), 61.1 (C-4), 52.3 (N–CHMe), 47.4, 41.1, 34.1 31.4, 24.8, 22.8, 22.1.20.5, 19.1.15.7 (menthoxy carbons and N–CHMe); GC–MS m/z = 451 [M^+]; Analysis calculated for $C_{27}H_{34}N_2O_4$: C, 71.97; H, 7.61; N, 6.22%. Found: C, 71.93; H, 7.64; N, 6.31%.

4.3.14. 3-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-4-(2-nitrophenyl)-1-((S)-1-phenylethyl)azetidin-2-one (**9l**)

Brown oil (Yield 43%); $[\alpha]_D^{25}$ = −48.43 (*c* 0.095, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 1751 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.98 (ArH d, 1H, *J* = 7.1), 7.22–7.63 (ArH, m, 8H), 5.23 (H-3, d, 1H, *J* = 5.1), 5.16 (H-4, d, 1H, *J* = 5.1), 4.51 (N–CHMe, q, 1H, *J* = 7.1), 3.12 (CH–O, menthoxy), 0.19–2.15 (H menthoxy, and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 169.1 (CO β-lactam), 148.8, 140.3, 132.7, 131.8130.3128.3, 127.8, 127.0, 126.8, 124.3 (aromatic carbons), 80.6 (CH–O, menthoxy), 59.4 (C-4), 54.3 (N–CHMe), 47.7, 41.2, 34.1, 31.2, 25.3.22.7, 22.1, 20.5.19.1, 15.2 (menthoxy carbons and N–CHMe), GC–MS m/z = 451 [M^+]; Analysis calculated for $C_{27}H_{34}N_2O_4$: C, 71.97; H, 7.61; N, 6.22%. Found: C, 71.91; H, 7.67; N, 6.26%.

4.3.15. 3-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-4-(naphthalen-2-yl)-1-((S)-1-phenylethyl)azetidin-2-one (**9m**)

Recrystallization from EtOAc. White solid (Yield 40%); Mp: 112–114 °C; $[\alpha]_D^{25}$ = +41.81 (*c* 0.022, $CHCl_3$); IR (KBr, cm^{-1}): 1751 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.68–7.82 (ArH, m, 4H), 7.45–7.49 (ArH, m, 3H), 7.22–7.33 (ArH, m, 5H), 5.14 (N–CHMe, q, 1H, *J* = 7.1), 4.78 (H-3, d, 1H, *J* = 4.8), 4.63 (H-4, d, 1H, *J* = 4.8), 2.81 (CH–O, menthoxy), 0.29–2.21 (H menthoxy, and N–CHMe, m, 21H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.6 (CO β-lactam), 139.7, 133.4, 133.0, 128.6, 128.0, 127.8, 127.7, 127.5, 127.4, 127.2126.3, 126.0 (aromatic carbons), 82.2 (C-3), 80.5 (CH–O, menthoxy), 62.0 (C-4), 51.6 (N–CHMe), 47.4, 40.8, 34.1, 31.4, 24.3, 22.7, 22.1, 20.4, 19.0, 15.1 (menthoxy carbons and N–CHMe), GC–MS m/z = 455 [M^+]; Analysis calculated for $C_{31}H_{37}NO_2$: C, 66.94; H, 7.07; N, 2.89%. Found: C, 66.99; H, 7.01; N, 2.97%.

4.4. General procedure for antimalarial activity measurements

The chloroquine resistant *P. falciparum* strain K14 (Southeast Asia) was cultured in vitro in a complete medium consisting of RPMI 1640 (In Vitrogen) supplemented with 27.5 mM $NaHCO_3$, 20 mg/L gentamycin, and 10% human serum [38]. Parasites were grown at 37 °C in human Oþ red blood cells at a 6% hematocrit under a 5% CO_2, 10% O_2, and 85% N_2 atmosphere. Cultures were synchronized by sorbitol treatments [39]. Stock solutions of lactam derivatives were prepared in sterile DMSO (10 mM) and later dilutions were with complete culture medium. Increasing concentrations of lactam derivatives (100 μL/well, top concentration = 50 μM) were distributed in a 96-well plate; DMSO (0.5% vol/vol, top concentration) was distributed for control. Then, 100 μL from a culture containing >95% ring (0–20 h postinvasion) at a 0.8% parasitemia and 3% hematocrit in complete medium was added per well along with 1.0 μCi of 3H-hypoxanthine with a specific activity of 14.1 Ci/mmol (Perkin–Elmer, Courtaboeuf, France). Parasites were grown for 42 h at 37 °C. Plates were then freeze-thawed and harvested on filters. Dried filters were moistened a in scintillation liquid mixture (Microscint O; Perkin–Elmer) and counted in a Top Count Microbeta counter (Perkin–Elmer). Percentage growth inhibition was calculated from the parasite associated radioactivity. 100% 3H-hypoxanthine incorporation was determined from a control grown in the absence of lactam derivatives. The concentration of drug giving 50% inhibition of label incorporation (IC_{50}) was determined by nonlinear regression analysis of log-based dose–response curve (Riasmart; Packard). Each concentration was estimated from independent experiments in triplicate.

Acknowledgments

The authors thank the Shiraz University Research Council for financial support (Grant No. 90-GR-SC-23).

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2014.09.077. These data include MOL files and InChiKeys of the most important compounds described in this article.

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