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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimalarial activity of new nanocopolymer β-lactams and molecular docking study of their monomers

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Abstract This report describes the preparation of some new β-lactam nanocopolymers. These nanoparticles are synthesized in water by emulsion polymerization of an acrylate β-lactam pre-dissolved in a mixture of co-monomers in the presence of sodium dodecyl sulfate as a surfactant and potassium persulfate as a radical initiator. Dynamic light scattering analysis and electron microscopy images of these emulsions show that the nanoparticles are approximately 30–70 nm in diameter. These compounds have been evaluated for their antimalarial activities against chloroquine-resistant *Plasmodium faliparum* K1 strain demonstrating IC_{50} varying from 14 to 50 μM. The interactions between these β-lactam nanocopolymers and the *P. falciparum* single-stranded DNA-binding proteins have been studied by molecular docking calculations.

Keywords β-Lactams · Nanoparticles · Polyacrylates · Emulsion polymerization · Molecular docking

Introduction

β-Lactams form a class of antibiotics characterized by the presence of a β-lactam (2-azetidinone) ring (George, 1992). This four-membered ring is responsible for biological activity in penicillins, cephalosporins, carbapenems, nocardicins and monobactams, which have been

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widely used as chemotherapeutic agents for treating microbial diseases (Marchand-Brynaert and Brule, 2008; Alcide *et al*., 2008; Halve and Bhadauria, 2007). Many other interesting biological properties, such as cholesterol absorption inhibitors (Rosenblum *et al*., 1998), human cytomegalovirus protease inhibitors (Borthwick *et al*., 1998), thrombin inhibitors (Han *et al*., 1995), anti-hyperglycemic (Goel *et al*., 2004), anti-tumor (Veinberg *et al*., 2004), anti-HIV (Sperka *et al*., 2005), anti-inflammatory, analgesic activities (Saturnino *et al*, 2000), antifungal (Zarei and Mohamadzadeh, 2011), antimalarial activities (Jarrahpour *et al*., 2014) and serine-dependent enzyme inhibitors, have been highlighted (Konaklieva, 2002). Moreover, β-lactams are very useful as key intermediates in organic synthesis (Ojima and Delaloge, 1997) and provide building blocks (Alcaide *et al*., 2007) for the construction of many nitrogen-containing organic molecules with fundamental biologically active novel compounds (Gerona-Navarro *et al*., 2003). Unfortunately, the microorganisms have developed resistance against β-lactam antibiotic drugs so organic chemists should design new β-lactam drugs displaying broader antibacterial activity (Fisher *et al*., 2005). So, many synthetic methods for synthesizing β-lactams are now available (Staudinger, 1907). The most convenient method for the construction of the β-lactam ring is the (2 + 2) cycloaddition of ketenes to imines known as the Staudinger reaction (Ebrahimi and Jarrahpour, 2014). The use of nanotechnology in medicinal chemistry has undergone rapid development in the last several decades (Peer *et al*., 2007). Nanomedicine is designed and synthesized drug delivery vehicles that can carry drug and efficiently cross physiological membranes to reach target sites (El-Ansary and Al-Daihan, 2009). The most quintessential nanoscale carriers include liposomes (Cavalcanti *et al*., 2005), polymeric nanoparticles (Langer, 1998), quantum dots (Smith *et al*., 2004), gold nanoparticles (Han *et al*., 2007), magnetic nanoparticles (McCarthy *et al*., 2007), carbon nanotubes (Jarrahpour *et al*., 2012), dendrimers, nucleic acid-based nanoconstructs (Jain and Asthana, 2007; Yevdokimov *et al*., 2005) and engineered viral nanoparticles (Singh *et al*., 2006). The aqueous solubility of poorly water-soluble drugs can be increased by using nanoemulsions. Enhanced drug solubility, perfect thermodynamic stability, ease of manufacturing and permeation over conventional formulations convert nanoemulsions to important drug delivery systems (Thakur *et al*., 2013). The unique properties of polymeric micelles as carriers of hydrophobic drugs have been reported in recent years (Lee *et al*., 2012). The preparation of different ampicillin (Fontana *et al*., 1998)-, amoxicillin (Fontana *et al*., 2001)- or penicillin (Henry-Michelland *et al*., 1987)-entrapped polycyanoacrylates and carbohydrate (Abeylath *et al*., 2008)- and antibiotic (Garay-Jimenez and Turos, 2011)-conjugated polyacrylate nanoparticles formed by emulsion polymerization in water has been reported. The preparation of polyacrylate-based nanoparticle emulsions that contain penicillin or *N*-thiolated β-lactam has been reported by Turos (Abeylath and Turos, 2007). These nanoparticles were prepared by free radical emulsion polymerization in water. Enhanced anti-MRSA activity of the nanoparticle polymers together with easy preparation and facile control of nanoparticle size are some advantages of these nanoparticles (Turos *et al*., 2007). Furthermore, the first in vivo study of the penicillin-conjugated nanoparticle emulsion has been reported (Greenhalgh and Turos, 2009). This report describes the synthesis of nanoparticle β-lactams based on well-precedent emulsion polymerization procedures. Docking studies are performed to propose a molecular target for these potential antimalarial compounds.

Experimental

General

All required chemicals were purchased from the Fluka, Merck and Acros chemical companies. CH_2Cl_2 and Et_3N were dried by distillation over CaH_2 and then stored over 4-Å molecular sieves. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 using a Bruker Avance DPX instrument (operating at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C). Chemical shifts were reported in ppm (δ) downfield from TMS. All the coupling constants (J) are in Hertz. IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. 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 a Buchi 510 melting point apparatus and are not corrected. The distribution morphology of the product was analyzed by CM10 transmission electron microscope (TEM; Philips 120 kV). Sample size and distribution of the products were checked by dynamic light scattering using a HORIBA DLS instrument. Column chromatography was performed on Merck Kieselgel (230–270 mesh). Thin-layer chromatography (TLC) was carried out on silica gel 254.

General procedure for the preparation of Schiff bases 2a–h

A mixture of amine **1a–d** (1.00 mmol) and aromatic aldehydes (1.00 mmol) was heated at reflux in ethanol (20 mL) for 5–6 h. Evaporation of the solvent afforded

imines **2a**–**h** as either oil or solid, which were used for the next step without further purification.

General procedure for the synthesis of *N*-substituted hydroxyl β-lactams 3a–h

A mixture of Schiff base **3a**–**h** (1.00 mmol) and triethylamine (7.00 mmol) in dry CH_2Cl_2 (15 mL) was stirred at 0 °C. Chlorotrimethylsilane (1.20 mmol) was added dropwise to the mixture and stirred for 1 h. Then, phenoxyacetic acid (1.50 mmol) and tosyl chloride (1.50 mmol) were added and the mixture was stirred at room temperature for 12 h. Then, it was washed with HCl 1 M (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was evaporated to give the crude β-lactams **3a**–**h**. Then, desired products were purified by silica gel column chromatography (eluent 8:2 petroleum ether:EtOAc) or recrystallization from EtOAc.

*1-(2-Hydroxylethyl)-4-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (**3a**)* Purified by column chromatography to give yellow oil (yield 87 %). IR (neat) cm^{-1}: 3415 (OH), 1758 (CO, β-lactam). ^{1}H NMR (DMSO) δ 2.74–2.99 (CH_2, m, 1H), 3.25–3.51 (CH_2, m, 3H), 3.62 (OMe, s, 3H), 4.81 (OH, t, 1H, $J = 4.2$ Hz), 5.12 (H-4, d, 1H, $J = 4.1$ Hz), 5.52 (H-3, d, 1H, $J = 4.1$ Hz), 6.66–6.92 (ArH, m, 5H), 7.11 (ArH, t, 2H, $J = 7.5$ Hz), 7.22 (ArH, d, 1H, $J = 8.2$ Hz). ^{13}C-NMR (DMSO) δ 42.5 (CH_2), 54.8 (OMe), 57.9 (CH_2), 60.9 (C-4), 81.2 (C-3), 113.3, 114.9, 121.4, 125.2, 129.2, 129.5, 156.5, 159.0 (aromatic carbons), 165.2 (CO β-lactam). MS $m/z = 313$ [M^+]. Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47 %. Found: C, 69.12; H, 6.25; N, 4.52 %.

*1-(2-Hydroxylethyl)-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (**3b**)* Recrystallized from EtOAc to give light yellow solid (yield 83 %). Mp: 80–82 °C. IR (KBr) cm^{-1}: 3382 (OH), 1766 (CO, β-lactam). ^{1}H NMR ($CDCl_3$) δ 3.05–3. 20 (CH_2, m, 1H), 3.31 (OH, s, 1H), 3.39–3.54 (CH_2, m, 1H), 3.78 (CH_2, s, 2H), 5.11 (H-4, d, 1H, $J = 4.4$ Hz), 5.51 (H-3, d, 1H, $J = 4.4$ Hz), 6.65 (ArH, d, 2H, $J = 7.9$ Hz), 6.84 (ArH, t, 1H, $J = 7.3$ Hz), 7.07 (ArH, t, 2H, $J = 6.9$ Hz), 7.47 (ArH, d, 2H, $J = 8.7$ Hz), 8.09 (ArH, d, 2H, $J = 8.7$ Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ 45.2 (CH_2), 59.6 (CH_2), 62.3 (C-4), 81.5 (C-3), 115.2, 122.5, 123.4, 129.3, 129.4, 140.6, 148.1, 156.2 (aromatic carbons), 166.4 (CO β-lactam). MS $m/z = 328$ [M^+]. Anal. Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53 %. Found: C, 62.28; H, 4.99; N, 8.61 %.

*1-(3-Hydroxylpropyl)-4-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (**3c**)* Recrystallized from EtOAc to give white solid (yield 80 %). Mp: 89–91 °C. IR (neat) cm^{-1}: 3417 (OH), 1735 (CO, β-lactam). ^{1}H NMR ($CDCl_3$) δ 1.44– 1.69 (CH_2, m, 2H), 2.87 (CH_2, dt, 1H, $J = 13.9$, 6.9 Hz), 3.27–3. 47 (CH_2, m, 3H), 3.63 (OMe, s, 3H), 4.46 (OH, t, 1H, $J = 4.8$ Hz), 5.06 (H-4, d, 1H, $J = 4.3$ Hz), 5.52 (H-3, d, 1H, $J = 4.3$ Hz), 6.78 (ArH, ddd, 5H, $J = 17.7$, 8.1, 0.8 Hz), 7.11 (ArH, dd, 2H, $J = 11.3$, 4.7 Hz), 7.16–7.31 (ArH, m, 2H). ^{13}C-NMR ($CDCl_3$) δ 30.1 (CH_2), 37.1 (CH_2), 54.8 (OMe), 58.1 (CH_2), 60.6 (C-4), 81.0 (C-3), 113.4, 114.9, 121.4, 125.5, 129.1, 129.6, 156.5, 159.0 (aromatic carbons), 165.0 (CO β-lactam). MS $m/z = 327$ [M^+]. Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28 %. Found: C, 69.79; H, 6.56; N, 4.35 %.

*1-(3-Hydroxylpropyl)-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (**3d**)* Recrystallized from EtOAc to give white solid (yield 83 %). Mp: 88–90 °C. IR (KBr) cm^{-1}: 3394 (OH), 1751 (CO, β-lactam). ^{1}H NMR ($CDCl_3$) δ 1.65–1.86 (CH_2, m, 2H), 2.58 (OH, s, 1H), 3.07–3.27 (CH_2, m, 1H), 3.82–3.57 (CH_2, m, 3H), 5.12 (H-4, d, 1H, $J = 4.1$ Hz), 5.52 (H-3, d, 1H, $J = 4.1$ Hz), 6.71 (ArH, d, 2H, $J = 8.4$ Hz), 6.90 (ArH, t, 1H, $J = 7.0$ Hz), 7.13 (ArH, t, 2H, $J = 7.7$ Hz), 7.53 (ArH, d, 2H, $J = 8.3$ Hz), 8.15 (ArH, d, 2H, $J = 8.1$ Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ 8.1 (CH_2), 37.4 (CH_2), 60.2 (CH_2), 60. 7 (C-4), 85.1 (C-3), 113.7, 115.3 121.9, 124.6, 128.0, 129.2, 129.9, 131.1, 156.8, 159.8 (aromatic carbons), 166.0 (CO β-lactam). MS $m/z = 342$ [M^+]. Anal. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18 %. Found: C, 63.24; H, 5.38; N, 8.15 %.

*Cis and trans 1-(4-hydroxylphenyl)-4-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (**3e**)* Recrystallized from EtOAc to give white solid (yield 91 %). Mp: 148–150 °C. IR (KBr) cm^{-1}: 3386 (OH), 1743 (CO, β-lactam). ^{1}H NMR (DMSO) δ 3.66 (OMe, s, 3H), 5.60 (H-4, d, 1H, $J = 4.6$ Hz), 5.70 (H-4, d, 1H, $J = 4.7$ Hz), 5.76 (H-3, d, 1H, $J = 4.6$ Hz), 5.85 (H-3, d, 1H, $J = 4.7$ Hz), 6.73 (ArH, d, 1H, $J = 8.8$ Hz), 6.83 (ArH, dd, 4H, $J = 8.5$, 3.3 Hz), 6.87–6.96 (ArH, m, 1H), 7.01 (ArH, d, 1H, $J = 8.7$ Hz), 7.18 (ArH, dd, 3H, $J = 16.3$, 8.0 Hz), 7.33 (ArH, dd, 3H, $J = 17.3$, 8.7 Hz), 9.44 (OH, s, 1H). ^{13}C-NMR (DMSO) δ 55.5 (OMe), 64.9 (C-4), 80.9 (C-3), 114.0, 114.9, 115.5, 118.7, 119.0, 121.8, 122.2, 123.1, 124.9, 125.3, 129.8, 135.1, 146.4, 154.6, 156.9, 159.6 8 (aromatic carbons), 163.2 (CO β-lactam). MS $m/z = 361$ [M^+]. Anal. Calcd. for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88 %. Found: C, 73.27; H, 5.41; N, 3.79 %.

*1-(4-Hydroxylphenyl)-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (**3f**)* Recrystallized from EtOAc to give white solid (yield 87 %). Mp: 204–206 °C. IR (KBr) cm^{-1}: 3393 (OH), 1751 (CO, β-lactam). ^{1}H NMR (DMSO) δ 5.63 (H-4, d, 1H, $J = 4.5$ Hz), 5.73 (H-3, d, 1H, $J = 4.5$ Hz), 6.77 (ArH, t, 4H, $J = 9.0$ Hz), 6.02–7.85 (ArH, m, 1H), 7.23–7.05 (ArH, m, 4H), 7.58 (ArH, d, 2H, $J = 8.0$ Hz),

8.10 (ArH, d, 2H, $J = 7.9$ Hz), 9.17 (OH, s, 1H). ^{13}C-NMR (DMSO) δ 60.2 (C-4), 80.5 (C-3), 114.8, 115.5, 118.2, 121.8, 121.9, 122.8, 128.1, 128.7, 128.9, 129.1, 140.6, 147.3, 154.3, 155.9 (aromatic carbons), 161.2 (CO β-lactam). MS $m/z = 376$ [M^+]. Anal. Calcd. for $C_{21}H_{16}N_2O_5$: C, 67.02; H, 4.29; N, 7.44 %. Found: C, 67.15; H, 4.37; N, 7.38 %.

*1-(4-(Hydroxylmethyl)phenyl)-4-(4-methoxyphenyl)-3-phenoxy azetidin-2-one (**3g**)* Purified by column chromatography to give yellow oil (yield 88 %). IR (neat) cm^{-1}: 3394 (OH), 1751 (CO, β-lactam). ^{1}H NMR ($CDCl_3$) δ 3.69 (OMe, s, 3H), 4.55 (CH_2, s, 2H), 4.62 (OH, s, 1H), 5.30 (H-4, d, 1H, $J = 4.8$ Hz), 5.46 (H-3, d, 1H, $J = 4.8$ Hz), 6.76 (ArH, d, 4H, $J = 8.6$ Hz), 6.82–7.00 (ArH, m, 2H), 7.05 (ArH, d, 1H, $J = 7.1$ Hz), 7.10–7.19 (ArH, m, 4H), 7.22–7.32 (ArH, m, 3H). ^{13}C-NMR ($CDCl_3$) δ 55.1 (OMe), 60.9 (CH_2), 65.3, 81.4, 115.6, 118.4, 121.8, 122.1, 123.4, 124.0, 128.0, 128.4, 128.0, 129.0, 133.0, 134.0, 139.9, 146.7, 148.2, 156.6 (aromatic carbons), 161.9 (CO β-lactam). MS $m/z = 375$ [M^+]. Anal. Calcd. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73 %. Found: C, 73.65; H, 5.70; N, 3.67 %.

*1-(4-(Hydroxylmethyl)phenyl)-4-(4-nitrophenyl)-3-phenoxyazeti din-2-one (**3h**)* Recrystallized from EtOAc to give white solid (yield 85 %). Mp: 126–128 °C. IR (KBr) cm^{-1}: 3417 (OH), 1751 (CO, β-lactam). ^{1}H NMR ($CDCl_3$) δ 4.53 (CH_2, s, 2H), 4.79 (OH, s, 1H), 5.67 (H-4, d, 1H, $J = 4.8$ Hz), 5.74 (H-3, d, 1H, $J = 4.8$ Hz), 6.78 (ArH, d, 2H, $J = 8.5$ Hz), 6.91 (ArH, t, 1H, $J = 7.4$ Hz), 7.05–7. 20 (ArH, m, 2H), 7.26 (ArH, d, 4H, $J = 2.6$ Hz), 7.56 (ArH, dd, 2H, $J = 8.8$, 2.4 Hz), 8.10 (ArH, dd, 2H, $J = 8.8$, 2.5 Hz). ^{13}C-NMR ($CDCl_3$) δ 45.7 (CH_2), 61.1 (C-4), 81.3 (C-3), 114.6, 115.3, 118.2, 118.3, 122.3, 122.6, 123.6, 127.5, 129.0, 129.5, 129.7, 133.0, 134.1, 140.1, 147.3, 148.1, 156.3 (aromatic carbons), 162.3 (CO β-lactam). MS $m/z = 390$ [M^+]. Anal. Calcd. for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18 %. Found: C, 68.76; H, 4.75; N, 7.06 %.

General procedure for the synthesis of acryloyloxy-Schiff bases (4a–h)

To the solution of imines **2a–h** (1.00 mmol) in 10 mL of CH_2Cl_2 was added triethylamine (2.20 mmol). Then, acryloyl chloride (2.20 mmol) was added dropwise to the solution at 0 °C. The resulting solution was stirred at room temperature for 30 min and then washed with H_2O (2 × 10 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and evaporated. The crude imines **4a–h** as either oil or solid were used for the next step without further purification.

*2-((4-Methoxybenzylidene)amino)ethyl acrylate (**4a**)* Yellow oil (yield 84 %). IR (neat) cm^{-1}: 1728 (CO, acrylate), 1650 (C=N). ^{1}H NMR ($CDCl_3$) δ 3.60–3.80 (CH_2, m, 4H), 3.92 (OMe, s, 3H), 5.60–5.70 (vinylic, m, 1H), 5.87 (vinylic, dt, 1H, $J = 3.10$, 1.10 Hz), 6.11 (vinylic, ddd, 1H, $J = 7.1$, 4.6, 1.9 Hz), 7.03 (ArH, d, 2H, $J = 15.0$ Hz), 7.84 (ArH, d, 1H, $J = 13.2$ Hz), 8.45 (CH=N, s, 1H). ^{13}C-NMR ($CDCl_3$) δ 38.9 (CH_2), 55.6 (OMe), 62.1 (CH_2), 111.8, 114.1, 119.8, 128.2, 131.8, 134.7 (aromatic and vinylic carbons), 160.91 (C=N), 164.17 (CO arylate). MS $m/z = 233$ [M^+]. Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00 %. Found: C, 67.11; H, 6.59; N, 5.88 %.

*2-((4-Nitrobenzylidene)amino)ethyl acrylate (**4b**)* Light yellow solid (yield 86 %). Mp: 61–63 °C. IR (KBr) cm^{-1}: 1751 (CO, acrylate), 1627 (C=N). ^{1}H NMR ($CDCl_3$) δ 3.70–4.07 (CH_2, m, 4H), 5.44–5. 68 (vinylic, m, 1H), 5.87–6.16 (vinylic, m, 1H), 6.27–6.56 (vinylic, m, 1H), 7.80–8.04 (ArH, m, 2H), 8.25 (ArH, dt, 2H, $J = 8.90$, 1.80 Hz), 8.42 (CH=N, s, 1H). ^{13}C-NMR ($CDCl_3$) $\delta = 38.9$ (CH_2), 63.4 (CH_2), 123.1, 123.7, 127.4, 129.0, 141.1, 149.1(aromatic and vinylic carbons), 160.7 (CH=N), 164.1 (CO acrylate). MS $m/z = 248$ [M^+]. Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29 %. Found: C, 58.21; H, 5.03; N, 11.12 %.

*3-((4-Methoxybenzylidene)amino)propyl acrylate (**4c**)* Yellow oil (yield 82 %). IR (neat) cm^{-1}: 1720 (CO, acrylate), 1650 (C=N). ^{1}H NMR ($CDCl_3$) δ 1.44–1.69 (CH_2, m, 2H), 2.74–2. 99 (CH_2, m, 1H), 3.25–3.51 (CH_2, m, 3H), 3.86 (OMe, s, 3H), 5.83–6.10 (vinylic, m, 1H), 5.16–6.39 (vinylic, m, 1H), 5.52–6.70 (vinylic, m, 1H), 7.01 (ArH, dt, 2H, $J = 4.4$, 2.6 Hz), 7.76–7.92 (ArH, m, 2H), 8.37 (CH=N, s, 1H). ^{13}C-NMR ($CDCl_3$) δ 27.1(CH_2), 36.1(CH_2), 55.7 (OMe), 60.9(CH_2), 123.7, 125.0, 127.5, 128.0, 130.5, 139.6, 144.0 (aromatic and vinylic carbons), 165.4 (C=N), 160.7 (CO arylate). MS $m/z = 247$ [M^+]. Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66 %. Found: C, 68.15; H, 7.05; N, 5.49 %.

*3-((4-Nitrobenzylidene)amino)propyl acrylate (**4d**)* Orange oil (yield 82 %). IR (neat) cm^{-1}: 1712 (CO, acrylate), 1650 (C=N). ^{1}H NMR ($CDCl_3$) δ 2.73–1. 13 (CH_2, m, 2H), 3.37 (CH_2, q, $J = 6.3$ Hz, 2H), 4.08–4.30 (CH_2, m, 2H), 5.57 (vinylic, ddd, 1H, $J = 9.8$, 2.0, 1.0 Hz), 5.68–5.90 (vinylic, m, 1H), 6.11 (vinylic, ddd, 1H, $J = 10.4$, 5.4, 1.0 Hz), 8.04 (ArH, d, 2H, $J = 9.8$ Hz), 8.34 (ArH, d, 2H, $J = 8.2$ Hz), 8.71 (CH=N, s, 1H), ^{13}C-NMR ($CDCl_3$) δ 25.5(CH_2), 36.1(CH_2), 61.2(CH_2), 124.2, 128.0, 129.6, 130.5, 140.2, 144.2 (aromatic and vinylic carbons), 160.1, (CH=N), 166.3 (CO acrylate). MS $m/z = 262$ [M^+]. Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68 %. Found: C, 59.63; H, 5.47; N, 10.55 %.

*4-((4-Methoxybenzylidene)amino)phenyl acrylate (**4e**)* Light brown oil (yield 93 %). IR (neat) cm^{-1}: 1729 (CO, acrylate), 1606 (C=N). ^1H NMR ($CDCl_3$) δ 3.86 (OMe, s, 3H), 5.83–6.10 (vinylic, m, 1H), 5.16–6.39 (vinylic, m, 1H), 5.52–6.70 (vinylic, m, 1H), 6.98 (ArH, dt, 3H, $J = 7.4$, 3.8 Hz), 7.11–7.24 (ArH, m, 3H), 7.76–7.95 (ArH, m, 2H), 8.37 (CH=N, s, 1H). ^{13}C-NMR ($CDCl_3$) δ 55.4 (OMe), 114.2, 114.3, 121.7, 122.1, 127.8, 128.1, 129.0, 130.5, 132.0, 132.6, 148.3, 149.9 (aromatic and vinylic carbons), 162.3 (CH=N), 164.3 (CO acrylate). MS $m/z = 281$ [M^+]. Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98 %. Found: C, 72.69; H, 5.51; N, 4.84 %.

*4-((4-Nitrobenzylidene)amino)phenyl acrylate (**4f**)* Orange solid (yield 94 %). Mp: 118–120 °C. IR (KBr) cm^{-1}: 1728 (CO, acrylate), 1627 (C=N). ^1H NMR ($CDCl_3$) δ 5.96–6.07 (vinylic, m, 1H), 6.26–6.42 (vinylic, m, 1H), 6.61 (vinylic, ddd, 1H, $J = 14.5$, 6.2, 2.0 Hz), 6.98 (ArH, dd, 3H, $J = 8.9$, 2.5 Hz), 7.12–7.24 (ArH, m, 3H), 7.79 – 7.88 (ArH, m, 2H), 8.38 (CH=N, s, 1H). ^{13}C-NMR ($CDCl_3$) δ 113.8, 115.6, 120.9, 121.2, 122.1, 127.7, 128.9, 130.9, 131.8, 133.0, 148.2, 150.1 (aromatic and vinylic carbons), 160.3, (CH=N), 164.4 (CO acrylate). MS $m/z = 296$ [M^+]. Anal. Calcd. for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46 %. Found: C, 64.97; H, 4.15; N, 9.35 %.

*4-((4-Methoxybenzylidene)amino)benzyl acrylate (**4g**)* Yellow oil (yield 87 %). IR (neat) cm^{-1}: 1728 (CO, acrylate), 1604 (C=N). ^1H NMR ($CDCl_3$) δ 3.89 (CH_2, s, 2H), 5.68–5.44 (vinylic, m, 1H), 6.16–5.87 (vinylic, m, 1H), 6.56–6.27 (vinylic, m, 1H), 6.73–7.10 (ArH, m, 4H), 7.13–7.48 (ArH, m, 4H), 7.84 (ArH, d, 1H, $J = 8.7$), 8.35 (CH=N, s, 1H). ^{13}C-NMR ($CDCl_3$) δ 55.4 (OMe), 65.6 (CH_2), 114.1, 127.8, 129.0, 130.6, 132.0, 137.4, 140.8, 159.8 (aromatic and vinylic carbons), 160.0 (CH=N), 165.7 (CO acrylate). MS $m/z = 295$ [M^+]. Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74 %. Found: C, 73.34; H, 5.96; N, 4.67 %.

*4-((4-Nitrobenzylidene)amino)benzyl acrylate (**4h**)* Orange solid (yield 94 %). Mp: 118–120 °C. IR (KBr) cm^{-1}: 1728 (CO, acrylate), 1627 (C=N). ^1H NMR ($CDCl_3$) δ 5.26 (CH_2, s, 2H), 5.84–5. 93 (vinylic, m, 1H), 6.07– 6. 27 (vinylic, m, 1H), 6.44 (vinylic, ddd, 1H, $J = 12.3$, 8.4, 3.6 Hz), 7.28 (ArH, dd, 2H, $J = 9.1$, 7.1 Hz), 7.45 (ArH, d, 1H, $J = 8.2$ Hz), 8.08 (ArH, d, 1H, $J = 7.9$ Hz), 8.27–8.38 (ArH, m, 2H), 8.56 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ 65.9 (CH_2), 119.9, 121.2, 124.3 128.1, 129.6 130.3, 130.9 134.7, 141.4, 150.8 157.6 (aromatic and vinylic carbons), 161.2 (CH=N), 166.3 (CO acrylate). MS $m/z = 310$ [M^+]. Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03 %. Found: C, 65.97; H, 4.66; N, 8.92 %.

General procedure for the synthesis of acrylate β-lactams 5a–h

A mixture of Schiff base **4a**–**h** (1.00 mmol), triethylamine (5.00 mmol), substituted acetic acids (1.50 mmol) and tosyl chloride (1.50 mmol) in dry CH_2Cl_2 (15 mL) was stirred at room temperature for overnight. Then, it was washed with HCl 1 M (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was evaporated to give the crude β-lactams **5a**–**h**. Then, desired products were purified by silica gel column chromatography (eluent 8:2 *n*-hexane/EtOAc) or recrystallization from EtOAc.

*2-(4-Methoxyphenyl)-4-oxo-3-phenoxyazetidin-1-yl)ethyl acrylate (**5a**)* Purified by column chromatography to give yellow oil (yield 81 %). IR (neat) cm^{-1}: 1758 (CO, β-lactam), 1720 (CO, acrylate). ^1H NMR ($CDCl_3$) δ 3.07 (CH_2, dt, 1H, $J = 14.0$, 6.8 Hz), 3.58 (CH_2, dt, 1H, $J = 17.6$, 7.3 Hz), 4.21 (CH_2, dd, 2H, $J = 12.7$, 6.4 Hz), 3.76 (OMe, s, 3H), 4.91 (H-4, d, 1H, $J = 4.3$ Hz), 5.40 (H-3, d, 1H, $J = 4.3$ Hz), 5.76–5.92 (vinylic, m, 1H), 6.10 (vinylic, td, 1H, $J = 17.2$, 11.5 Hz), 6.28–6.51 (vinylic, m, 1H), 6.73 (ArH, d, 2H, $J = 8.6$ Hz), 6.82 (ArH, d, 2H, $J = 11.4$ Hz), 7.12 (ArH, t, 2H, $J = 9.2$ Hz), 7.21–7.32 (ArH, m, 3H). ^{13}C-NMR ($CDCl_3$) δ 37.7(CH_2), 55.1 (OMe), 62.5 (CH_2), 67.5 (C-4), 82.1 (C-3), 113.7, 114.6, 115.5, 121.9, 124.6, 125.8, 128.1, 129.2, 129.8, 129.9, 131.1, 156.9, 159.9 (aromatic and vinylic carbons), 161.9 (CO, β-lactam), 166.1 (CO acrylate). MS $m/z = 367$ [M^+]. Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81 %. Found: C, 68.71; H, 5.82; N, 3.76 %.

*2-(4-Nitrophenyl)-4-oxo-3-phenoxyazetidin-1-yl)ethyl acrylate (**5b**)* Recrystallization from EtOAc to give white solid (yield 85 %). Mp: 120–122 °C. IR (KBr) cm^{-1}: 1766 (CO, β-lactam), 1728 (CO, acrylate). ^1H NMR ($CDCl_3$) δ 3.31 (CH_2, ddd, 1H, $J = 15.0$, 6.4, 3.3 Hz), 3.89 (CH_2, ddd, 1H, $J = 11.8$, 10.8, 8.0 Hz), 4.17 (CH_2, ddd, 1H, $J = 11.8$, 6.4, 3.5 Hz), 4.31–4. 48 (CH_2, m, 1H), 5.17 (H-4, d, 1H, $J = 4.6$ Hz), 5.52 (H-3, d, 1H, $J = 4.5$ Hz), 5.81–5.92 (vinylic, m, 1H), 6.03 (vinylic, ddd, 1H, $J = 17.1$, 10.4, 0.4 Hz), 6.29–6.48 (vinylic, m, 1H), 6.71 (ArH, d, 2H, $J = 7.9$ Hz), 6.90 (ArH, t, 1H, $J = 7.4$ Hz), 7.14 (ArH, dd, 1H, $J = 8.4$, 7.5 Hz), 7.52 (ArH, d, 2H, $J = 8.7$ Hz), 8.15 (ArH, d, 2H, $J = 8.6$ Hz). ^{13}C-NMR ($CDCl_3$) δ 39.9 (CH_2), 61.2 (CH_2), 62.0 (C-4), 82.3 (C-3), 115.2, 122.4, 123.4, 127.4, 129.3, 129.4, 132.0, 140.7, 148.1, 156.3 (aromatic and vinylic carbons), 165.6 (CO, β-lactam), 165.7 (CO acrylate). MS $m/z = 382$ [M^+]. Anal. Calcd. for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.75; N, 7.33 %. Found: C, 62.91; H, 4.83; N, 7.25 %.

*2-(4-Methoxyphenyl)-4-oxo-3-phenoxyazetidin-1-yl)propyl acrylate (**5c**)* Purified by column chromatography to give yellow oil (yield 80 %). IR (neat) cm^{-1}: 1766 (CO, β-lactam), 1728 (CO, acrylate). ^1H NMR ($CDCl_3$) δ 1.88 (CH_2, dd, 2H, $J = 13.3$, 6.7 Hz), 2.96– 3.17 (CH_2, m, 2H), 3.73 (OMe, s., 3H), 4.16 (CH_2, t, 2H, $J = 6.2$ Hz), 4.94 (H-4, d, 1H, $J = 4.3$ Hz), 5.42 (H-3, d, 1H, $J = 4.3$ Hz), 5.81 (vinylic, dd, 1H, $J = 10.4$, 1.5 Hz), 5.96–6.19 (vinylic, m, 1H), 6.36 (vinylic, dt, 1H, $J = 4.5$, 2.3 Hz), 6.66–6.94 (ArH, m, 5H), 7.12 (ArH, dd, 2H, $J = 9.9$, 5.9 Hz), 7.26 (ArH, dd, 2H, $J = 8.5$, 3.6 Hz). ^{13}C-NMR ($CDCl_3$) δ 7.9 (CH_2), 37.4 (CH_2), 55.1 (OMe), 61.7 (CH_2), 62.0 (C-4), 81.7 (C-3), 113.7, 115.3, 121.9, 124.6, 128.0, 129.1, 129.8, 129.9, 131.1, 157.0, 159.8 (aromatic and vinylic carbons), 166.4 (CO, β-lactam), 169.7 (CO acrylate). MS $m/z = 381$ [M^+]. Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67 %. Found: C, 69.37; H, 6.15; N, 3.51 %.

*2-(4-Nitrophenyl)-4-oxo-3-phenoxyazetidin-1-yl)propyl acrylate (**5d**)* Recrystallization from EtOAc to give white solid (yield 78 %). Mp: 98–100 °C. IR (KBr) cm^{-1}: 1751 (CO, β-lactam), 1725 (CO, acrylate). ^1H NMR ($CDCl_3$) δ 1.77–2.13 (CH_2, m, 2H), 3.01–3.25 (CH_2, m, 2H), 4.21 (CH_2, dd, 2H, $J = 9.8$, 5.6 Hz), 5.13 (H-4, d, 1H, $J = 4.3$ Hz), 5.54 (H-3, d, 1H, $J = 4.4$ Hz), 5.74–5.93 (vinylic, m, 1H), 6.08 (vinylic, ddd, 1H, $J = 17.3$, 10.4, 1.1 Hz), 6.26–6.46 (vinylic, m, 1H), 6.72 (ArH, dd, 2H, $J = 7.7$, 0.9 Hz, 2H), 6.81–6.99 (ArH, m, 1H), 6.96–7.36 (ArH, m, 2H), 7.40–7.66 (ArH, m, 2H), 8.01–8.36 (ArH, m, 2H). ^{13}C-NMR ($CDCl_3$) δ 8.4 (CH_2), 38.0 (CH_2), 61.5 (CH_2), 61.6 (C-4), 82.1 (C-3), 115.2, 122.4, 123.4, 127.9, 129.4, 131.3, 140.8, 148.1, 156.3 (aromatic and vinylic carbons), 165.5 (CO, β-lactam), 165.9 (CO acrylate). MS $m/z = 396$ [M^+]. Anal. Calcd. for $C_{21}H_{20}N_2O_6$: C, 63.63; H, 5.09; N, 7.07 %. Found: C, 63.75; H, 5.21; N, 7.01 %.

*2-(4-Methoxyphenyl)-4-oxo-3-phenoxyazetidin-1-yl)phenyl acrylate (**5e**)* Purified by column chromatography to give color less oil (yield 87 %). IR (neat) cm^{-1}: 1751 (CO, β-lactam), 1704 (CO, acrylate). ^1H NMR ($CDCl_3$) δ 3.73 (OMe, s, 3H), 5.33 (H-4, d, 1H, $J = 4.8$ Hz), 5.52 (H-3, d, 1H, $J = 4.8$ Hz), 5.90–6.06 (vinylic, m, 1H), 6.26 (vinylic, ddd, 1H, $J = 17.3$, 10.1, 1.6 Hz), 6.48–6.65 (vinylic, m, 1H), 6.73–6.85 (ArH, m, 3H), 6.95–7.06 (ArH, m, 3H), 7.09–7.22 (ArH, m, 2H), 7.23–7.43 (ArH, m, 5H). ^{13}C-NMR ($CDCl_3$) $\delta = 55.1$ (OMe), 61.8 (C-4), 81.3 (C-3), 113.9, 114.8, 114.9, 115.3, 115.6, 118.4, 121.0, 122.0, 122.1, 122.2, 127.6, 127.8, 129.2, 129.4, 129.6, 129.9, 132.8, 146.8, 156.9, 159.9 (aromatic and vinylic carbons), 163.0 (CO, β-lactam), 164.5 (CO acrylate). MS $m/z = 415$ [M^+]. Anal. Calcd. for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.10; N, 3.37 %. Found: C, 72.36; H, 5.05; N, 3.31 %.

*2-(4-Nitrophenyl)-4-oxo-3-phenoxyazetidin-1-yl)phenyl acrylate (**5f**)* Purified by column chromatography to give light yellow oil (yield 83 %). IR (neat) cm^{-1}: 1751 (CO, β-lactam), 1720 (CO, acrylate). ^1H NMR ($CDCl_3$) δ 5.54 (H-4, d, 1H, $J = 4.9$ Hz), 5.67 (H-3, d, 1H, $J = 4.9$ Hz), 6.01 (vinylic, dd, 1H, $J = 10.4$, 0.8 Hz), 6.28 (vinylic, ddd, 1H, $J = 17.2$, 10.3, 0.7 Hz), 6.58 (vinylic, dd, 1H, $J = 17.7$, 1.7 Hz), 6.78 (ArH, d, 2H, $J = 8.6$ Hz), 6.95 (ArH, d, 1H, $J = 6.9$ Hz), 7.00–7.11 (ArH, m, 2H), 7.17 (ArH, t, 2H, $J = 7.8$ Hz), 7.34 (ArH, q, 2H, $J = 2.8$ Hz), 7.55 (ArH, d, 2H, $J = 8.6$ Hz), 8.13 (ArH, d, 2H, $J = 8.2$ Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ 61.1 (C-4), 81.3 (C-3), 114.6, 115.3, 118.2, 118.3, 122.0, 122.3, 122.6, 123.6, 127.5 129.0, 129.5 129.7, 133.0, 134.1, 140.1, 147.3, 148.1, 156.3 (aromatic and vinylic carbons), 162.3 (CO, β-lactam), 164.4 (CO acrylate). MS $m/z = 430$ [M^+]. Anal. Calcd. for $C_{24}H_{18}N_2O_6$: C, 66.97; H, 4.22; N, 6.51 %. Found: C, 67.05; H, 4.15; N, 6.68 %.

*2-(4-Methoxyphenyl)-4-oxo-3-phenoxyazetidin-1-yl)benzyl acrylate (**5g**)* Purified by column chromatography to give light yellow oil (yield 83 %). IR (neat) cm^{-1}: 1751 (CO, β-lactam), 1720 (CO, acrylate). ^1H NMR ($CDCl_3$) δ 3.73 (OMe, s, 3H), 4.59 (CH_2, s, 2H), 5.33 (H-4, d, 1H, $J = 4.8$ Hz), 5.52 (H-3, d, 1H, $J = 4.8$ Hz), 5.90–6.06 (vinylic, m, 1H), 6.29 (vinylic, dt, 1H, $J = 17.3$, 9.3 Hz), 6.65–6.50 (vinylic, m, 1H), 6.80 (ArH, dd, 4H, $J = 11.7$, 5.5 Hz), 6.85–6.97 (ArH, m, 3H), 7.03 (ArH, dt, 3H, $J = 6.8$, 3.8 Hz), 7.07–7.22 (ArH, m, 3H). ^{13}C-NMR ($CDCl_3$) δ 55.1 (OMe), 61.8 (CH_2), 67.7 (C-4), 81.3 (C-3), 113.9, 114.6, 114.8, 114.9, 115.3, 115.6, 118.4, 121.0 122.0 122.1, 122.2, 124.0, 127.6, 127.7, 127.8, 129.2, 129.4, 129.5, 129.6, 129.9, 132.8, 134.7 146.8, 156.9, 159.9 (aromatic and vinylic carbons), 163.03 (CO, β-lactam), 164.0 (CO acrylate). MS $m/z = 429$ [M^+]. Anal. Calcd. for $C_{26}H_{23}NO_5$: C, 72.71; H, 5.40; N, 3.26 %. Found: C, 72.85; H, 5.55; N, 3.30 %.

*2-(4-Nitrophenyl)-4-oxo-3-phenoxyazetidin-1-yl)benzyl acrylate (**5h**)* Recrystallized from EtOAc to give white solid (yield 79 %). Mp: 130–132 °C. IR (KBr) cm^{-1}: 1743 (CO, β-lactam), 1704 (CO, acrylate). ^1H NMR ($CDCl_3$) δ 4.59 (CH_2, s, 2H), 5.33 (H-4, d, 1H, $J = 4.8$ Hz), 5.52 (H-3, d, 1H, $J = 4.8$ Hz), 5.90–6.06 (vinylic, m, 1H), 6.26 (vinylic, ddd, 1H, $J = 17.3$, 10.1, 1.6 Hz), 6.48–6.65 (vinylic, m, 1H), 6.73–6.85 (ArH, m, 2H), 6.95–7.06 (ArH, m, 2H), 7.09 –7.22 (ArH, m, 3H), 7.23–7.43 (ArH, m, 6H). ^{13}C-NMR ($CDCl_3$) δ 61.8 (CH_2), 67.4 (C-4), 87.3 (C-3), 114.0, 115.3, 115.6, 118.7, 120.9 122.4, 124.0, 127.0, 127.7, 129.2, 129.9, 132.4, 134.6, 147.3, 157.2 (aromatic and vinylic carbons), 163.1 (CO, β-lactam), 164.7 (CO acrylate). MS $m/z = 444$ [M^+]. Anal. Calcd. for

$C_{25}H_{20}N_2O_6$: C, 67.56; H, 4.54; N, 6.30 %. Found: C, 67.68; H, 4.63; N, 6.21 %.

Preparation of the polyacrylate nanoparticle emulsions (6a–h)

Experimental procedure for the emulsion copolymerization

Poly (butyl acrylate–styrene) nanoparticles were prepared by emulsion polymerization. β-Lactams **5a**–**h** (10 mg, 1 % w/w) were dissolved in a 7:3 (w/w) mixture of butyl acrylate (700 mg) and styrene (300 mg) at 70 °C and heated for 10 min under Ar atmosphere. Deionized water (4.0 mL) was then added to the solution, followed by appropriate amount of sodium dodecyl sulfate (10 mg) and potassium persulfate (5 mg) as surfactant and radical initiator, respectively. The mixture was then stirred for 7 h at 70 °C and cooled to room temperature. The samples were purified and characterized to determine their shape and average size. Purification of the above emulsion was performed by continuous extraction using ethyl acetate followed by centrifugation on a bench-top centrifuge, and then, samples were filtered with cellulose acetate membrane (200 nm).

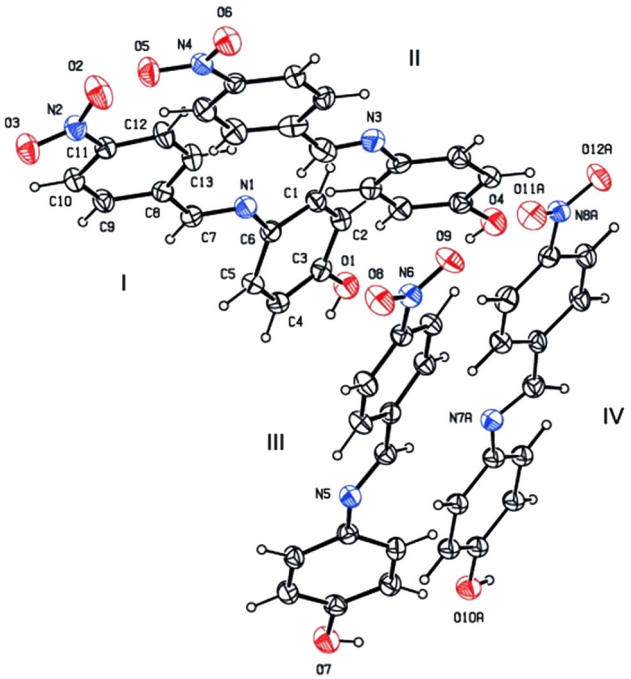


Fig. 1 ORTEP diagram of imine **2f**

Characterization of the emulsions of prepared nanoparticles

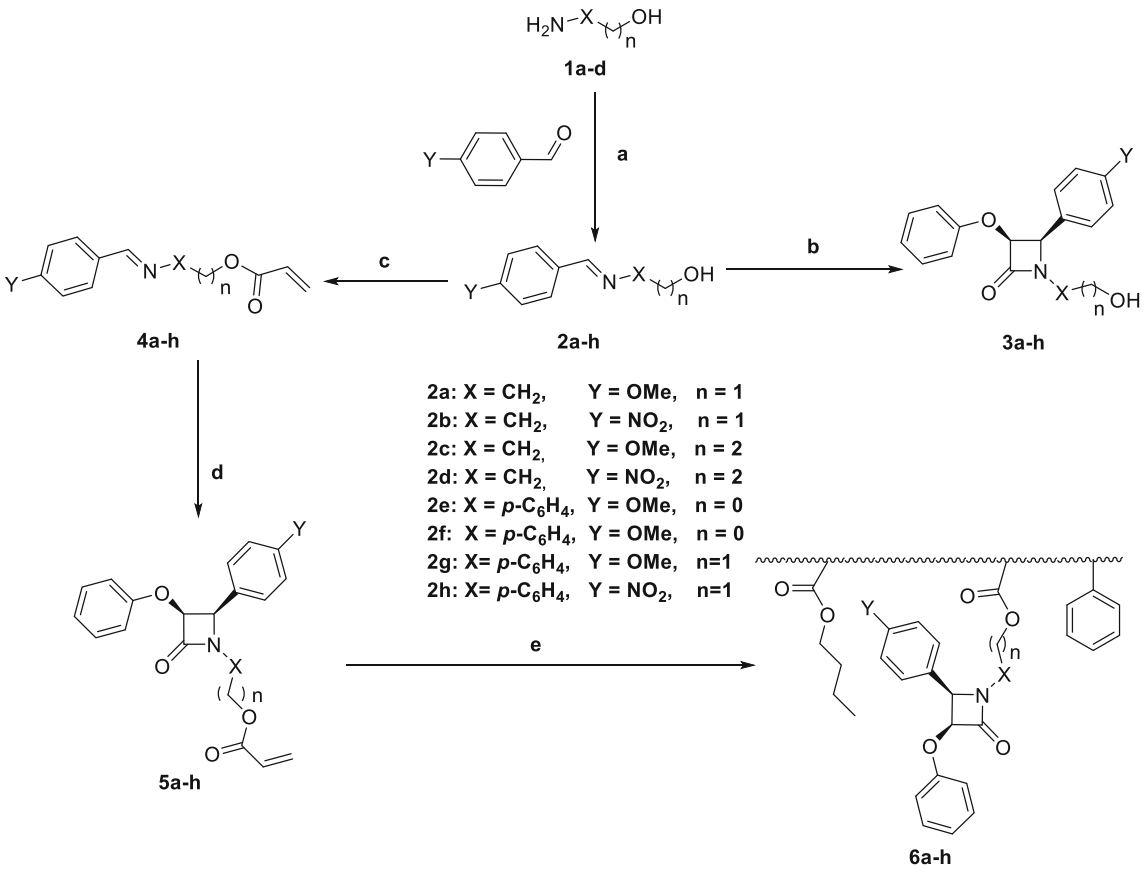
Sample size and distribution of the emulsions were checked by dynamic light scattering (DLS) using a HORIBA DLS instrument equipped with a laser beam at 550 nm. The sample was pre-diluted with distilled water (0.3 mL of emulsion in 24.7 mL of water). Transmission electron microscopy (TEM) of the samples was captured by placing a drop of diluted emulsion (1 mL of emulsion in 10 mL of the distilled water and sonicated) onto a Formvar-coated copper grid and evaporating the solvent by air blowing, and then, the grid was viewed on the microscope.

General procedure for antimalarial activity measurements

The chloroquine-resistant *P. falciparum* strain K1 (Southeast Asia) was in vitro cultured in complete medium consisting of RPMI 1640 (In Vitrogen) supplemented with 27.5 mM $NaHCO_3$, 20 mg/L gentamycin and 10 % human serum. Parasites were grown at 37 °C in human O^+ 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 (Noedl *et al*., 2005). Stock solutions of lactam derivatives were prepared in sterile DMSO (10 mM), and later dilutions were done 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 post invasion) at a 0.8 % parasitemia and 3 % hematocrit in complete medium was added per well. The plates were incubated at 37 °C in the presence of 5 % CO_2, 85 % N_2 and 10 % O_2 for 72 h. After culture the plates were frozen down at −20 °C. Parasite growth inhibition was quantified using a homemade HRP2 ELISA assay based on *Pf* HRP2 detection (Lemkul and Bevan, 2012). Drug concentrations inhibiting parasite growth by 50 % (IC_{50}) were calculated by nonlinear regression analysis from the dose–response relationship as fitted by software—ICEstimator 1.2 (http://www.antimalarial-icestimator.net) (Nagard *et al*., 2011; Kaddouri *et al*., 2006). Each concentration was estimated from independent experiments in triplicate.

Results and discussion

In this study, some free hydroxyl imines **2a**–**h** (Chackalamannil *et al*., 2010; Hosseini-Sarvari, 2011; Peng *et al*., 2007; Bae *et al*., 2012; Müller *et al*., 2010; Murphy-Jolly *et al*., 2010) were synthesized from aliphatic and aromatic



Scheme 1 Synthesis of *N*-substituted hydroxy β-lactams **3a–h**, acrylate β-lactam monomers **5a–h** and copolymer **6a–h** by emulsion polymerization. Reagents and conditions: **a** EtOH, reflux; **b** 1. TMSiCl, Et_3N, CH_2Cl_2, 1 h, 2. $PhOCH_2CO_2H$, TsCl, 12 h; **c** acryloyl chloride, Et_3N, CH_2Cl_2, 0.5 h; **d** $PhOCH_2CO_2H$, Et_3N, CH_2Cl_2, TsCl, 15 h; **e** SDS, $K_2S_2O_8$, n-butyl acrylate, styrene, H_2O, 70 °C, 7 h

amines containing the hydroxyl group **1a–d** and aromatic aldehydes in refluxing ethanol (Scheme 1). The X-ray crystallography of **2f** confirmed the E stereochemistry (Fig. 1) (Atioglu *et al*., 2015).

To prepare β-lactams **3a–h**, hydroxy imines **2a–h** were protected by trimethylsilyl chloride (TMSCl) in the presence of Et_3N in dry CH_2Cl_2 (Cossfo *et al*., 1986). Then, phenoxyacetic acid and *p*-toluenesulfonyl chloride were added to the above crude mixture. The new mixture was stirred for 12 h to afford *N*-substituted hydroxy β-lactams **3a–h** in good to excellent yields. The silyl group was deprotected during aqueous workup (Scheme 1).

The cycloadducts of N-substituted hydroxy β-lactams **3a–h** were characterized by spectral analyses (Table 1). As a model, in the IR spectrum of **3a**, the absorption for the hydroxy group was exhibited at 3415 cm^{-1}. A sharp band at 1758 cm^{-1} was assigned to the stretching frequency of β-lactam carbonyl, which is a proof of the β-lactam ring (Fig. 2a). The ^{1}H-NMR spectrum of **3a** displayed a multiplet for the two methylene groups at 2.74–2.99 (m, 1H), 3.25–3.51 (m, 3H), a singlet at 3.62 for the methoxy protons and the hydroxyl proton as a triplet at 4.81 (t, $J = 4.2$ Hz, 1H) ppm. The β-lactam H-3 and H-4 protons appeared as two doublets at 5.52 ppm and 5.12, respectively. The observed coupling constants of these protons confirmed the *cis* stereochemistry for this compound. Aromatic protons showed a multiplet, a triplet and a doublet at 6.66–6.92, 7.11 and 7.22, respectively. The ^{13}C-NMR spectrum of compound **3a** displayed the β-lactam carbonyl peak at 165.2 ppm. In addition, the carbon of aliphatic part, methoxy group, C-4 and C-3 of β-lactam ring appeared at 42.5, 57.9, 54.8, 60.9 and 81.2 ppm, respectively.

Acrylated β-lactam monomers **5a–h** were synthesized from acrylated-imines **4a–h** in the presence of phenoxyacetic acid, tosyl chloride and triethylamine in dry CH_2Cl_2. The IR spectrum of **5a** showed a sharp band at 1758 cm^{-1} for the β-lactam carbonyl and an absorption at 1720 cm^{-1} for the carbonyl of the acrylate (Fig. 2b). The disappearance of the hydroxyl peak also confirmed the success of the protection by the acroyl group. The ^{1}H-NMR spectrum of **5a** exhibited a singlet peak at 3.76 which is due to the methoxy protons. The ethyl part of the molecule showed two doublets of triplets at 3.07 and 3.58. The β-lactam H-3

Table 1 Structures of β-lactams **3a–h** and **5a–h**

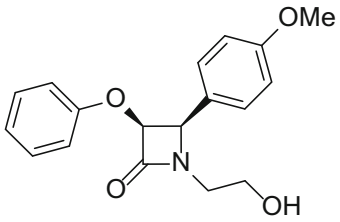
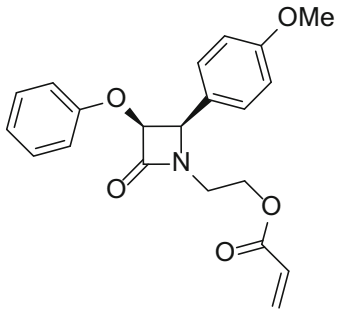
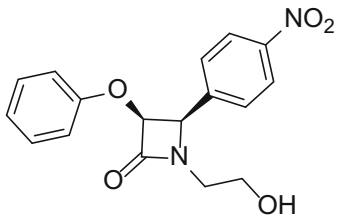
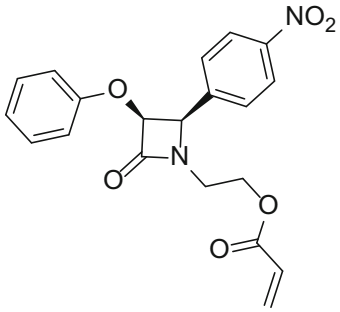
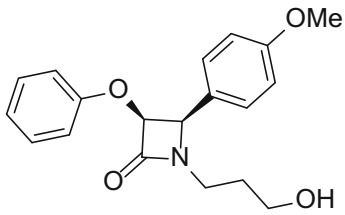
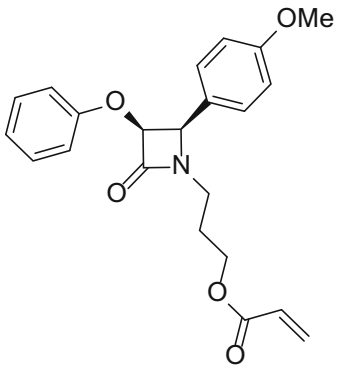
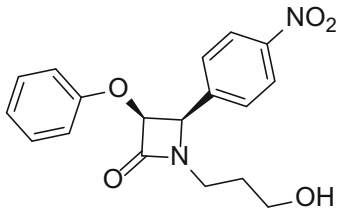
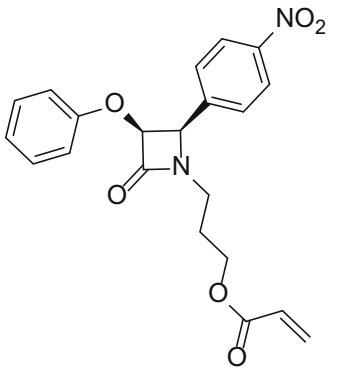
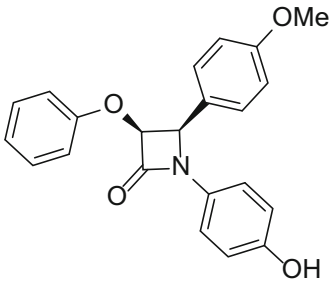
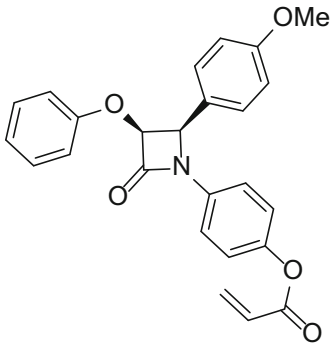
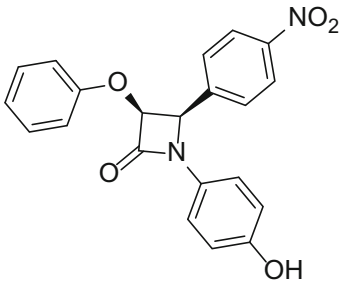
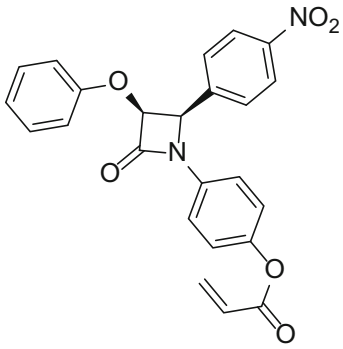
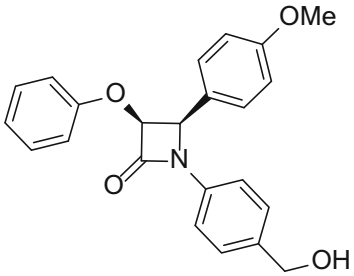
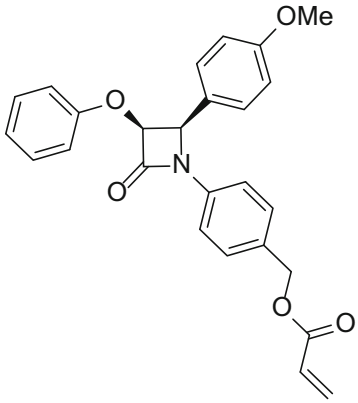
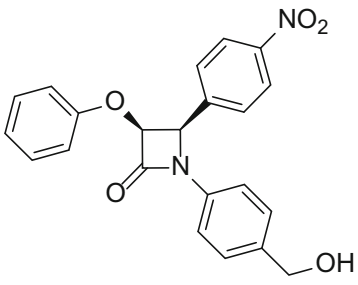
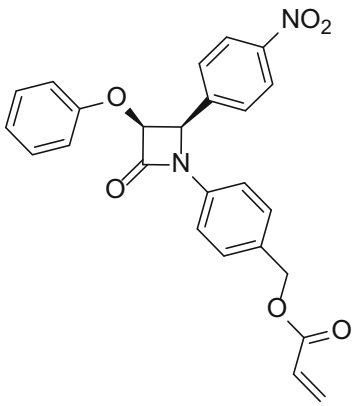
β-Lactam	Structure	Yield (%)	β-Lactam	Structure	Yield (%)
3a		87	**5a**		81
3b		83	**5b**		85
3c		80	**5c**		80
3d		81	**5d**		78

Table 1 continued

β-Lactam	Structure	Yield (%)	β-Lactam	Structure	Yield (%)
3e		91	**5e**		87
3f		87	**5f**		83
3g		88	**5g**		81
3h		85	**5h**		79

and H-4 protons exhibited two doublets at 5.40 and 4.91, respectively. The observed coupling constants ($J = 4.3$ Hz) for H-4 and ($J = 4.3$ Hz) for H-3 confirmed the *cis* stereochemistry for this compound. The vinylic protons were observed as a multiplet at 5.92–5.76 (vinylic, m, 1H), 6.10 (td, $J = 17.2$, 11.5 Hz, 1H), 6.28– 6.51 (m, 1H). Aromatic protons showed two doublets, a triplet and a multiplet at 6.73 (d, $J = 8.6$ Hz, 2H), 6.82 (d, $J = 11.4$ Hz, 2H), 7.12 (t, $J = 9.2$ Hz, 2H) and 7.21–7.32 (m, 3H) ppm, respectively. The ^{13}C-NMR spectrum of **5a** displayed the β-lactam and acryloyl carbonyl signals at 161.9 and 166.1 ppm, respectively. In addition, the carbon of methoxy group, C-4 and C-3 of β-lactam ring appeared at 55.1, 67.5 and 82.1 ppm, respectively.

In the next step, the acrylated β-lactam monomers **5a**–**h** were used for the preparation of β-lactam nanocopolymers **6a**–**h**. These nanocopolymeric emulsions were prepared easily in water by radical initiator emulsion polymerization using warmed mixture of butyl acrylate, styrene and an acrylated β-lactam monomer (Jarrahpour and Heiran, 2014). For this, the acrylated β-lactam monomers **5a**–**h** were dissolved in a mixture of butyl acrylate and styrene 7:3 (w:w) at 70 °C under Ar atmosphere. Then, the mixture was pre-emulsified in deionized water and sodium dodecyl sulfate (SDS) (1 % w) was added as the surfactant. After about 30 min, the homogenous solution was treated with potassium persulfate (0.5 % w/w) to start free radical polymerization for 7 h (Scheme 1). After that, for the purification the nanopolymeric emulsions were extracted with ethyl acetate followed by centrifuging on a bench-top centrifuge to remove minor impurities such as excess surfactant or residual monomers, without changing the physical characteristics of the nanoparticles in the emulsion. Finally, to remove any particles bigger than 200 nm the samples were filtered with cellulose acetate membrane (0.2 μm).

The IR spectrum of nanocopolymer **6a** showed the characteristic absorption of C=O acrylate at 1724 and C=O β-lactam at 1743 cm^{-1} (Fig. 2c). The morphology and the particle size analyses of the emulsions were performed by TEM and DLS. DLS analyses of the final emulsion showed that the average diameter of the **6a**–**h** were regularly about 50, 39, 58, 58, 29, 26, 58, 44 nm, respectively, with size distributions spanning from about 10–230 nm. The average diameter of nanocopolymeric emulsions **6e**–**h** bearing an aromatic ring at the N-1 position of the β-lactam ring is less than the aliphatic ones **6a**–**d** (Fig. 3).

TEM image of **6a** is shown in Fig. 4, and it is seen that the nanoparticles are essentially spherical and their sizes are about 30–70 nm.

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 *S. aureus* and Gram-negative bacteria *E. coli* or *P. aeruginosa* with MICs superior to 50 μM. Nevertheless, moderate antimalarial activities have been obtained against chloroquine-resistant *P. falciparum* K1 strain as outlined in Table 2 with IC_{50} varying from 14 to 50 μM. On the other hand, a strong influence of the groups

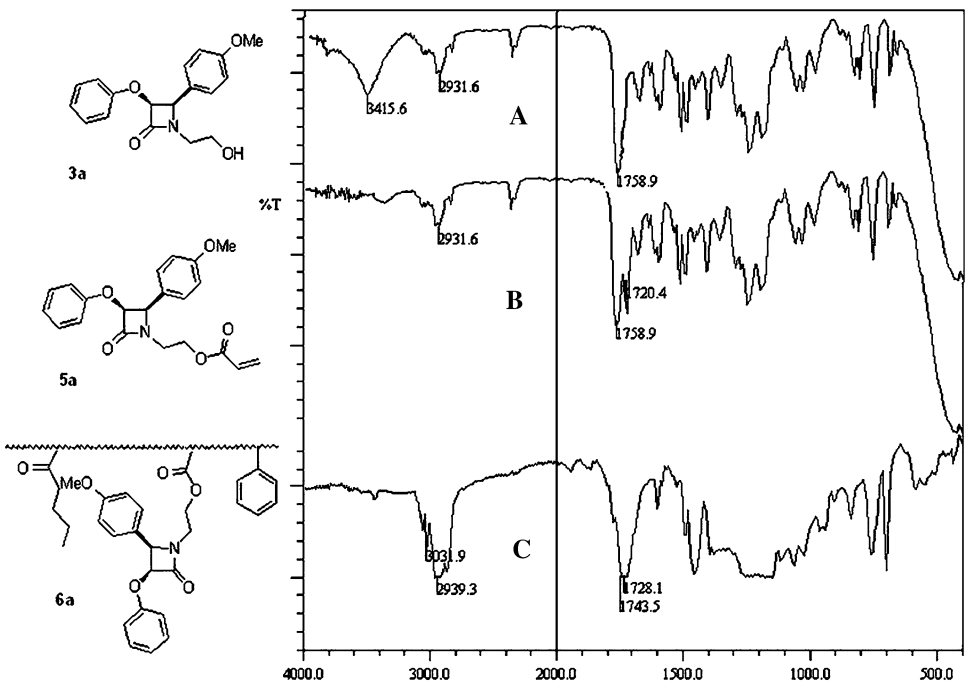


Fig. 2 The IR spectrum of **a** *N*-substituted hydroxyl β-lactam **3a**, **b** acrylated β-lactam monomer **5a**, **c** β-lactam nanocopolymer **6a**

bearing on the nitrogen atom of the considered derivative is noted. Moreover, nanopolymeric emulsions present activities in a similar range with their monomers.

Structure activity relationship (SAR) study of β-lactams reveals that the methoxyphenyl on C-4 of β-lactam ring (**3e** and **3g**) enhances the antimalarial activity. Also the phenolic 2-azetidinones (**3e** and **3f)** and those bearing the benzyl alcohol moiety **(3g** and **3h)** showed more activity than the aliphatic alcohols.

Molecular docking

Molecular docking technique is used to predict the bound conformations of organic ligands into a protein target of known structure. This technique is becoming increasingly more important and is extremely cost-effective in drug discovery because of its ability to quickly screen libraries of compounds that may potentially act as drugs. Docking methods usually use an energy-based scoring function to identify the energetically most favorable ligand–protein binding. The calculated energy of interaction is reflective of the affinity of the ligand for binding to the macromolecule active site. The lower energy scores represent better protein–ligand bindings compared to higher energy values (Lemkul and Bevan, 2012). Proteins–ligand complexes can be considered as an ensemble of representative conformational structures, and the binding events may undergo a wide range of motions in the ensemble structures ranging from small changes in binding site residues to large-scale motions of entire protein (Verkhivker *et al*., 2002).

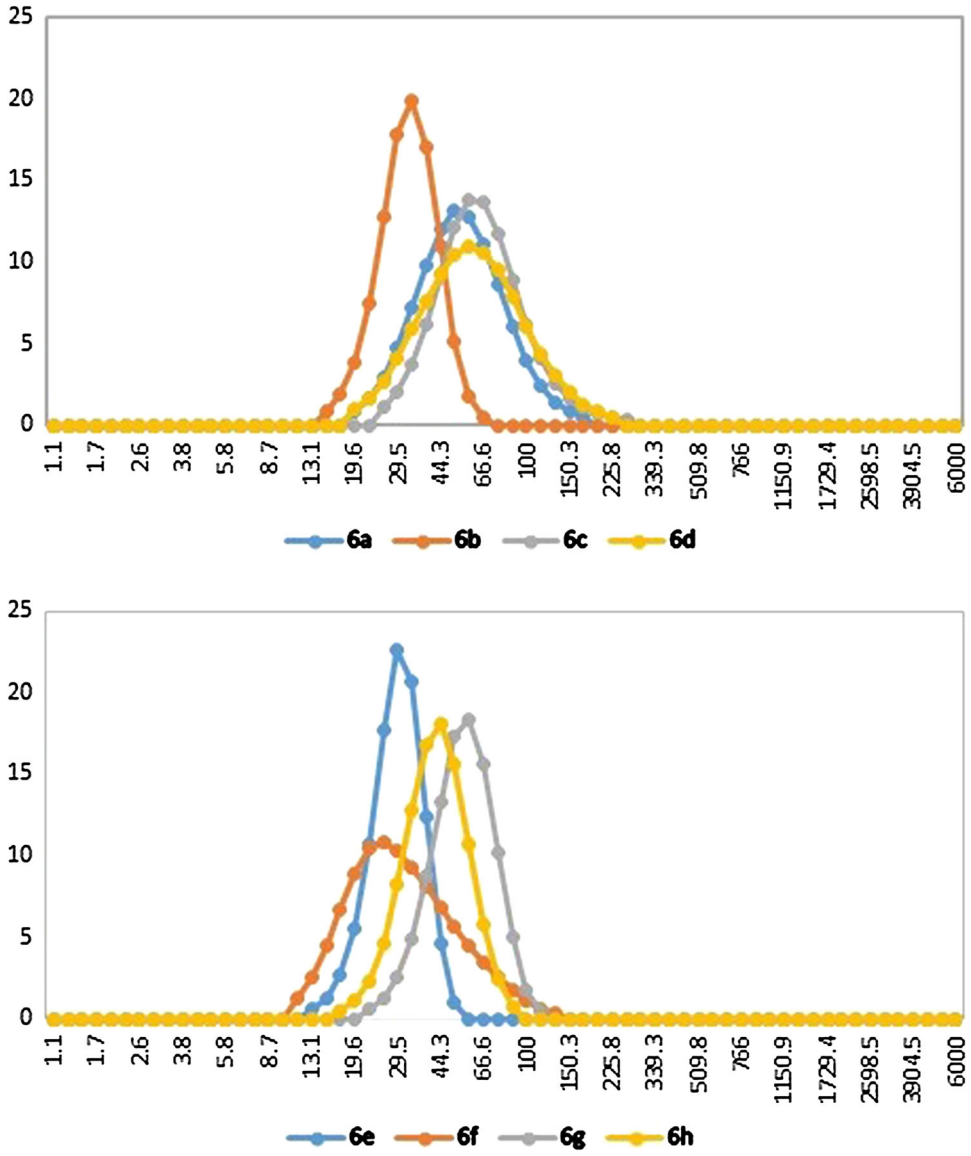


Fig. 3 DLS analyses of **6a–h**

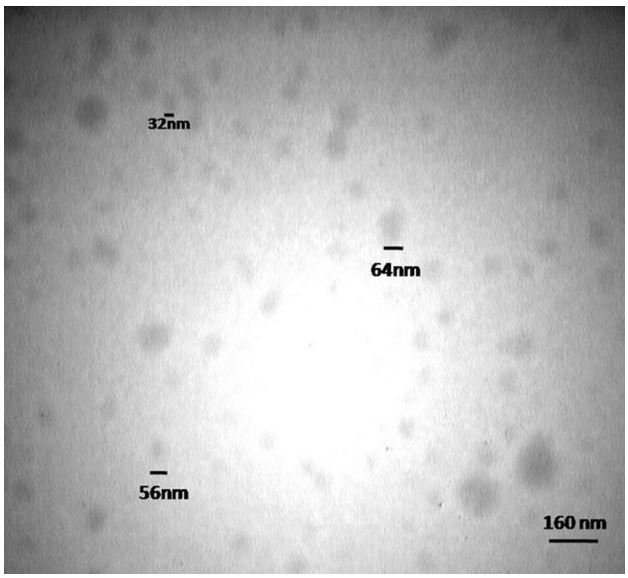


Fig. 4 TEM image of **6a**

Efficient development of new therapeutics for targeting *Plasmodium falciparum* K1 requires detailed information about the mechanism of action of these compounds. Information obtained from molecular docking simulations will likely accelerate the process of novel antimalarial drug development.

The single-stranded DNA-binding (SSB) protein from *P. falciparum* [*P. falciparum* SSB (*Pf*-SSB)] is encoded in the nucleus and transported to the apicoplast where it likely functions in the replication and maintenance of the apicoplast genome. SSB proteins are present in nearly all organisms and bind to single-stranded DNA (ssDNA) intermediates produced transiently during replication, repair and recombination.

Therefore, we have performed docking to study the probable interaction between our synthetic compounds and *Pf*-SSB. Docking is usually carried out in two steps: the generation of configurations of the ligand in the binding site and the energetic scoring of those configurations (poses) to determine their favorability. It requires high-quality structures of a receptor molecule, typically an enzyme or receptor protein to which the ligand will bind. The candidate drug molecule may be treated as flexible, while the receptor is predominantly rigid, though most modern algorithms allow for a subset of residues to be treated as flexible, as well.

Atomic coordinates for the three-dimensional protein models (a crystal structure at 2.1 Å resolution of the *Pf*-SSB tetramer bound to two $(dT)_{35}$ molecules; PDB code 3ULP) (Antony *et al*., 2012) are obtained from the Protein Data Bank "(http://www.rcsb.org/pdb/) DNA residues," and all crystallographic waters are removed from the atomic coordinate data files.

The structures of the compounds used in this study (see Table 1) were optimized at the B3LYP/6-31G* level of theory by using Gaussian 03 program (Frisch *et al*., 2009). The Autodock Vina program (Trott and Olson, 2010) was used to study the binding of the **3a–h** and **5a–h** to the *Pf*-SSB tetramer. The docking energies are calculated from a set of energy grids centered in the active site of the enzyme. The protein coordinates are fixed during calculations, while the inhibitor is flexible and moves on the grid. Grid searching was performed by genetic algorithm to locate the ligand in the best binding orientation and conformation based on the binding energy.

The results revealed that the best inhibitor is **3g** with a docking energy of −130 kcal/mol, while **3e** was slightly less potent (with a docking energy of −128 kcal/mol). Docking energies of the **3a–h** compounds ranged from −27 to −130 kcal/mol. These results are in accordance with the IC_{50} variations. The same trends are also observed for **5a–h** compounds. For instance, the docking energy of **5g** compound is about −38 kcal/mol less than that of **3g** due to lack of fit in the cavity of the target protein. The lowest energy models of **3g** and **5g** bound to *Pf*-SSB tetramer are shown in Fig. 5a and 5b. A hydrogen bond between **3g** and Asn28 of *Pf*-SSB tetramer is shown in Fig. 5b.

Table 2 Antimalarial activities of derivatives **3a–h**, **5a–h** and **6a–6h** against chloroquine-resistant *Plasmodium falciparum* K1 strain

Product	IC_{50} (μM)	Product	IC_{50} (μM)	Product	IC_{50} (μM)
Chloroquine	0.804				
3a	>50	**5a**	>50	**6a**	>50
3b	>50	**5b**	>50	**6b**	>50
3c	33	**5c**	39	**6c**	30
3d	36	**5d**	32	**6d**	29
3e	14	**5e**	27	**6e**	27
3f	21	**5f**	30	**6f**	36
3g	14	**5g**	25	**6g**	22
3h	19	**5h**	20	**6h**	39

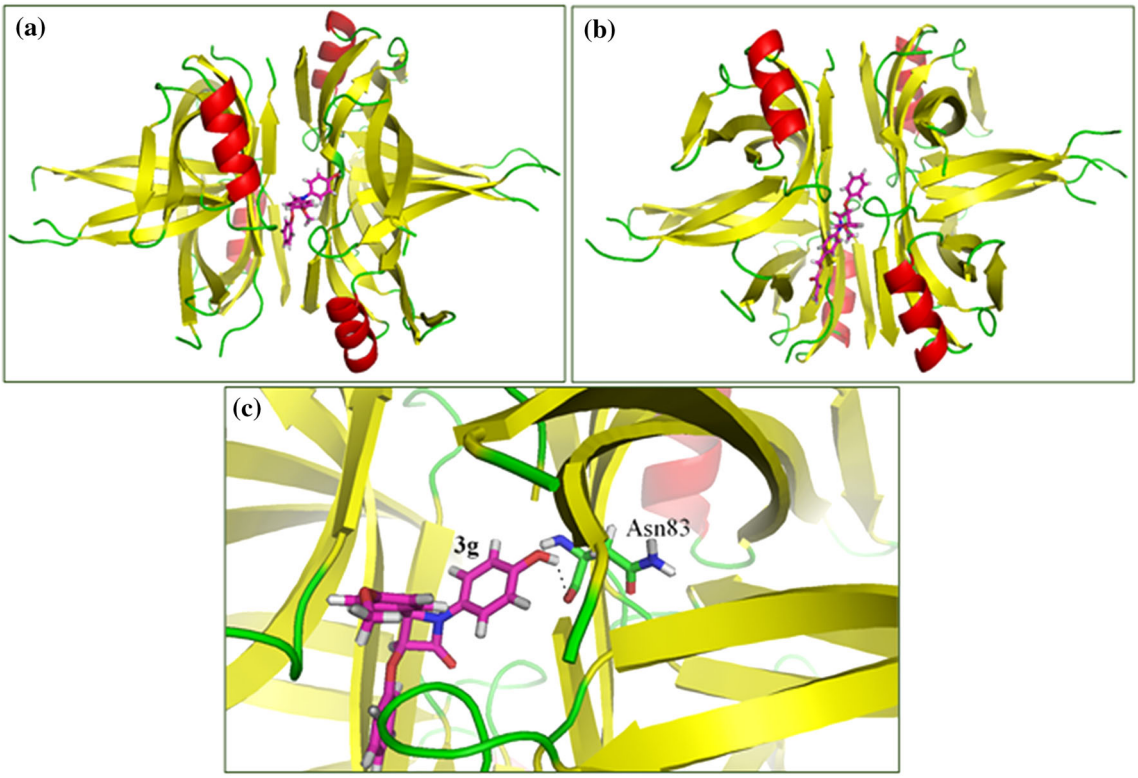


Fig. 5 One mode of binding of **a 3g** and **b 5g** to the *Pf*-SSB tetramer. **c** A hydrogen bond between **3g** and Asn83 of *Pf*-SSB tetramer is shown as black dashed line

Conclusions

In this study, several nanopolyacrylate β-lactams have been synthesized from the corresponding monomeric β-lactams by emulsion polymerization. The polyacrylated β-lactam nanoparticles showed average diameter of 26–58 nm. Finally, moderate antimalarial activities were obtained against chloroquine-resistant *P. falciparum* K1 strain with IC_{50} varying from 14 to up to 50 μM. Structure activity relationship study of β-lactams revealed that the methoxyphenyl group enhances the antimalarial activity, while those bearing the phenolic and the benzyl alcohol moieties showed more activity than the aliphatic alcohols.

Molecular docking results showed that these compounds could create crucial hydrogen bonding and hydrophobic interactions to the *Pf*-SSB tetramer within protein binding pocket.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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