J IRAN CHEM SOC
DOI 10.1007/s13738-013-0277-6

ORIGINAL PAPER

Synthesis of new nanocopolymer containing β-lactams

Aliasghar Jarrahpour · Roghayeh Heiran

Received: 16 April 2013 / Accepted: 17 May 2013

Abstract Several new monocyclic β-lactam monomers bearing the NO_2 group **2a–g** were synthesized via a [2 + 2] ketene–imine cycloaddition reaction (Staudinger reaction). Calculation of coupling constant of H-3 and H-4, and the X-ray crystallography of β-lactam **2e** confirmed the *cis* stereochemistry of these β-lactams. Then aminophenyl β-lactams were synthesized by the reduction of NO_2 to NH_2 group in the presence of Raney Ni and hydrazine hydrate. Treatment of these aminophenyl β-lactams with acryloyl chloride and sodium bicarbonate ($NaHCO_3$), afforded the monomers bearing the $NHCOCH{=}CH_2$ group. These acrylated β-lactam monomers were dissolved in a warm mixture of butyl acrylate and styrene and then were converted to the corresponding polyacrylate nano β-lactams by emulsion polymerization in water. A unique feature of this methodology is the ability to incorporate water-insoluble compounds directly into the nanoparticle framework. Structures of the synthesized compounds were confirmed by physical and spectral analyses. Dynamic light scattering analysis and transmission electron microscopy of the final emulsions show that the nanoparticles were about 50–70 nm in diameter.

Keywords 2-Azetidinone · [2 + 2] Cycloaddition · Staudinger reaction · Polyacrylate nanoparticles

Introduction

2-Azetidinones (β-lactams) show a wide range of activity on different pathogens and a considerable research has been done on the synthesis of new potent antifungal and antibacterial 2-azetidinones [1, 2]. The biological activity of the 2-azetidinone framework is believed to be associated with the chemical reactivity of 2-azetidinone ring and on the substituents, especially at nitrogen of the 2-azetidinone ring [3]; therefore, functionalization of the 2-azetidinone framework is significant for the development of new β-lactam antibiotics [4].

The body distribution, effectiveness, and specificity of a drug can be modified when it is incorporated within a carrier. In recent years, there have been a number of efforts on the development of polymeric micelles as carriers of hydrophobic drugs because of their unique properties [5–8].

Nano-delivery systems of appropriate stability, size, and surface properties offer the possibility of increasing the therapeutic index of the known or new drug molecules by increasing their efficiency and decreasing their toxicity against physiological tissues [9, 10].

Several groups have reported on the preparation and antibacterial testing of different ampicillin- or penicillin-entrapped polycyanoacrylates, carbohydrate- and antibiotic-conjugated polyacrylate nanoparticles formed by anionic emulsion polymerization in water [11–17].

Turos et al. [6, 7, 16, 17] have reported the preparation and in vitro microbiological properties of polyacrylate-based nanoparticle emulsions that contain water-insoluble antibiotic drugs, such as penicillin or N-thiolated β-lactam. These nanoparticles were prepared by free radical emulsion polymerization in water. Easy preparation, facile control of nanoparticle size, and enhanced anti-MRSA activity of the nanoparticle polymers versus the nonpolymerized form were some essential features of these nanoparticles. In this paper, we report the synthesis of some new nano β-lactams.

A. Jarrahpour (✉) · R. Heiran
Department of Chemistry, College of Sciences,
Shiraz University, 71454 Shiraz, Iran
e-mail: jarrah@susc.ac.ir

Published online: 26 June 2013

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-d6 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 analytical sheets obtained from Fluka.

General procedure for the preparation of Schiff bases **1a–g**

A mixture of a substituted aniline (10.0 mmol) and an aromatic aldehyde (10.0 mmol) was refluxed in ethanol for appropriate time. After cooling of solution, the precipitate was filtered and washed with ethanol to afford Schiff bases **1a–g**.

General procedure for the synthesis of β-lactams **2a–g**

A mixture of Schiff base (1.00 mmol), triethylamine (5.00 mmol), acetic acid derivative (1.5 mmol) and *p*-toluenesulfonyl chloride (1.5 mmol) in dry CH_2Cl_2 (50 mL) was stirred at room temperature overnight. After the reaction completion (TLC monitoring), the mixture was washed with HCl (1 N), saturated sodium bicarbonate solution, brine, dried (Na_2SO_4) and the solvent was evaporated under vacuum to afford the crude β-lactams **2a–g**. Then they were purified by recrystallization from EtOAc.

1-(4-Methoxyphenyl)-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (2a)

Light yellow crystals from EtOAc (yield 64 %); mp: 142–144 °C; IR (KBr, cm^{-1}): 1,352, 1,521 (NO_2), 1,770 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$)δ (ppm): 3.68 (OMe, s, 3H), 5.87 (H-4, d, $J = 5.0$ Hz, 1H), 5.93 (H-3, d, $J = 5.0$ Hz, 1H), 6.79–8.13 ArH, m, 13H); ^{13}C-NMR δ (ppm) 55.2 (OMe), 59.9 (C-4), 80.7 (C-3), 114.6, 115.0, 118.4, 122.0, 123.2, 129.4, 129.4, 129.7, 141.3, 148.1, 156.1, 156.1 (aromatic carbons), 161.7 (CO, β-lactam); GC–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, 67.65; H, 4.61; N, 7.16 %.

3-(2,4-Dichlorophenoxy)-1-(4-methoxyphenyl)-4-(4-nitrophenyl)azetidin-2-one (2b)

White crystals from EtOAc (yield 61 %); mp: 196–198 °C; IR (KBr, cm^{-1}): 1,346, 1,521 (NO_2), 1,754 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.70 (OMe, s, 3H), 5.43 (H-4, d, $J = 5.0$ Hz, 1H), 5.48 (H-3, d, $J = 5.0$ Hz, 1H), 6.74–8.18 (ArH, m, 11H); ^{13}C-NMR δ (ppm): 55.5 (OMe), 60.5 (C-4), 81.9 (C-3), 114.7, 116.8, 118.8, 123.7, 124.1, 127.7, 128.1, 129.0, 129.6, 130.1, 140.0, 148.0, 151.2, 157.0 (aromatic carbons), 161.3 (CO, β-lactam); GC–MS $m/z = 458$ [M+]; Anal. calcd for $C_{22}H_{16}Cl_2N_2O_5$: C, 57.53; H, 3.51; N, 6.10 %. Found: C, 57.53; H, 3.49; N, 6.11 %.

3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)-4-(4-nitrophenyl)azetidin-2-one (2c)

White crystals from EtOAc (yield 66 %); mp: 128–130 °C; IR (KBr, cm^{-1}): 1,349, 1,527 (NO_2), 1,749 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.76 (OMe, s, 3H), 5.47 (H-4, d, $J = 4.9$ Hz, 1H), 5.57 (H-3, d, $J = 4.9$ Hz, 1H), 6.73–8.20 (ArH, m, 12H); ^{13}C-NMR δ (ppm) 55.5 (OMe), 60.9 (C-4), 81.3 (C-3), 114.6, 116.8, 118.7, 123.7, 127.7, 128.9, 129.4, 129.7, 140.3, 148.2, 155.1, 156.9 (aromatic carbons), 161.5 (CO, β-lactam); GC–MS $m/z = 424$ [M+]; Anal. calcd for $C_{22}H_{17}ClN_2O_5$: C, 62.20; H, 4.03; N, 6.59 %. Found: C, 62.19; H, 4.00; N, 6.59 %.

3-(2,4-Dichlorophenoxy)-1-(4-methoxyphenyl)-4-(3-nitrophenyl)azetidin-2-one (2d)

White crystals from EtOAc (yield 53 %); mp: 156–158 °C; IR (KBr, cm^{-1}): 1,344, 1,522 (NO_2), 1,763 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.76 (OMe, s, 3H), 5.51 (H-4, d, $J = 5.1$ Hz, 1H), 5.56 (H-3, d, $J = 5.1$ Hz, 1H), 6.82–8.29 (ArH, m, 11H); ^{13}C-NMR δ (ppm) 55.5 (OMe), 60.4 (C-4), 81.6 (C-3), 114.7, 116.6, 118.8, 123.3, 123.9, 127.7, 127.9, 129.7, 129.7, 130.0, 130.1, 133.9, 135.0, 148.3, 151.1, 156.9 (aromatic carbons), 161.3 (CO, β-lactam); GC–MS $m/z = 458$ [M+]; Anal. calcd for $C_{22}H_{16}Cl_2N_2O_5$: C, 57.53; H, 3.51; N, 6.10 %. Found: C, 57.50; H, 3.52; N, 6.10 %.

1-(4-Methoxyphenyl)-4-(3-nitrophenyl)-3-phenoxyazetidin-2-one (2e)

White crystals from EtOAc (yield 47 %); mp: 142 °C; IR (KBr, cm^{-1}): 1,350, 1,527 (NO_2), 1,739 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.75 (OMe, s, 3H), 5.48 (H-4, d, $J = 4.8$ Hz, 1H), 5.63 (H-3, d, $J = 4.8$ Hz, 1H), 6.75–8.23 (ArH, m, 13H); ^{13}C-NMR δ (ppm) 55.5 (OMe), 61.0 (C-4), 81.0 (C-3), 114.6, 115.4, 118.8, 122.6, 123.3, 123.8, 129.5, 129.5, 129.8, 133.9, 135.4, 148.1, 156.4, 156.8 (aromatic carbons), 161.9 (CO, β-lactam); GC–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, 67.65; H, 4.61; N, 7.16 %.

1-(4-Methoxyphenyl)-3-(naphthalen-2-yloxy)-4-(3-nitrophenyl)azetidin-2-one (2f)

Light green powder from EtOAc (yield 72 %); mp: 158 °C; IR (KBr, cm^{-1}): 1,342, 1,527 (NO_2), 1,743 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.76 (OMe, s, 3H), 5.53 (H-4, d, $J = 4.8$ Hz, 1H), 5.74 (H-3, d, $J = 4.8$ Hz, 1H), 6.82–8.28 (ArH, m, 15H); ^{13}C-NMR δ (ppm) 55.5 (OMe), 61.0 (C-4), 81.0 (C-3), 109.1, 114.6, 118.0, 118.8, 123.2, 123.8, 124.5, 126.7, 126.9, 127.6, 129.5, 129.6, 129.8, 129.8, 133.8, 133.9, 135.34, 148.2, 154.3, 156.9 (aromatic carbons), 161.8 (CO, β-lactam); GC–MS $m/z = 440$ [M+]; Anal. calcd for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36 %. Found: C, 70.93; H, 4.56; N, 6.35 %.

1-(4-Chlorophenyl)-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (2 g)

White powder from EtOAc (yield 51 %); mp: 206–208 °C; IR (KBr, cm^{-1}): 1,350, 1,527 (NO_2), 1,743 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.50 (H-4, d, $J = 4.9$ Hz, 1H), 5.66 (H-3, d, $J = 4.9$ Hz, 1H), 6.76–8.19 (ArH, m, 13H); ^{13}C-NMR δ (ppm); 60.1 (C-4), 80.9 (C-3), 115.0, 118.7, 122.1, 123.2, 128.3, 128.3, 128.3, 129.4, 135.1, 140.7, 147.4, 156.0 (aromatic carbons), 162.5 (CO, β-lactam); GC–MS $m/z = 394$ [M+]; Anal. calcd for $C_{21}H_{15}ClN_2O_4$: C, 63.89; H, 3.83; N, 7.10 %. Found: C, 63.86; H, 3.84; N, 7.11 %.

General procedure for the synthesis of β-lactams 3a–g

β-Lactams **2a**–**g** (1 mmol) was dissolved in 80 mL of EtOH: H_2O (9:1) by heating to reflux. Then the temperature was reduced to 60 °C and hydrazine hydrate (2.34 mmol) and Raney-Ni (1 g) were added. The mixture was refluxed for several minutes until complete conversion of β-lactams **2a**–**g** to **3a**–**g** (TLC monitoring). The cold mixture was filtered and the solvent was evaporated under the reduced pressure. The crude products were purified by silica gel chromatography (eluent 5:1 $CHCl_3$/EtOAc) to yield pure β-lactams **3a**–**g**.

4-(4-Aminophenyl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (3a)

White crystal purified by column chromatography (eluent 5:1 $CHCl_3$/EtOAc) (yield 63 %); mp: 150–152 °C; IR (KBr, cm^{-1}): 1,736 (CO, β-lactam), 3,361, 3,446 (NH_2); ^{1}H-NMR (DMSO) δ (ppm): 3.66 (OMe, s, 3H), 5.03 (NH_2, s, 2H), 5.43 (H-4, d, $J = 4.5$ Hz, 1H), 5.67 (H-3, d, $J = 4.5$ Hz, 1H), 6.36–7.48 (ArH, m, 13H); ^{13}C-NMR δ (ppm); 55.1 (OMe), 61.1 (C-4), 80.4 (C-3), 113.4, 114.3, 115.0, 118.4, 119.1, 121.5, 128.9, 129.2, 130.2, 148.6, 155.7, 156.6 (aromatic carbons), 162.2 (CO, β-lactam); GC–MS $m/z = 360$ [M+]; Anal. calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77 %. Found: C, 73.29; H, 5.57; N, 7.79 %.

4-(4-Aminophenyl)-3-(2,4-dichlorophenoxy)-1-(4-methoxyphenyl)-azetidin-2-one (3b)

White crystal purified by column chromatography (eluent 5:1 $CHCl_3$/EtOAc) (yield 67 %); mp: 150–152 °C; IR (KBr, cm^{-1}): 1,757 (CO, β-lactam), 3,372, 3,458 (NH_2); ^{1}H-NMR (DMSO) δ (ppm): 3.67 (OMe, s, 3H), 5.06 (NH_2, s, 2H), 5.46 (H-4, d, $J = 4.3$ Hz, 1H), 5.82 (H-3, d, $J = 4.3$ Hz, 1H), 6.36–7.42 (ArH, m, 11H); ^{13}C-NMR δ (ppm); 55.1 (OMe), 59.7 (C-4), 80.4 (C-3), 113.4, 114.3, 115.0, 115.0, 118.4, 119.1, 121.5, 128.9, 129.2, 129.2, 130.2, 148.6, 155.7, 156.6 (aromatic carbons), 162.2 (CO, β-lactam); GC–MS $m/z = 428$ [M+]; Anal. calcd for $C_{22}H_{18}Cl_2N_2O_3$: C, 61.55; H, 4.23; N, 6.53 %. Found: C, 61.49; H, 4.25; N, 6.55 %.

4-(4-Aminophenyl)-3-(4-chlorophenoxy)-1-(4-methoxyphenyl)-azetidin-2-one (3c)

White powder purified by column chromatography (eluent 5:1 $CHCl_3$/EtOAc) (yield 63 %); mp: 150–152 °C; IR (KBr, cm^{-1}): 1,745 (CO, β-lactam), 3,388, 3,475 (NH_2); ^{1}H-NMR (DMSO) δ (ppm): 3.67 (OMe, s, 3H), 5.07 (NH_2, s, 2H), 5.44 (H-4, d, $J = 4.5$ Hz, 1H), 5.70 (H-3, d, $J = 4.5$ Hz, 1H), 6.37–7.23 (ArH, m, 12H); ^{13}C-NMR δ (ppm); 55.1 (OMe), 60.9 (C-4), 80.4 (C-3), 113.4, 114.4, 116.7, 118.50, 118.8, 125.2, 128.8, 128.9, 130.1, 148.7, 155.3, 155.7 (aromatic carbons), 161.8 (CO, β-lactam); GC–MS $m/z = 394$ [M+]; Anal. calcd for $C_{22}H_{19}ClN_2O_3$: C, 66.92; H, 4.85; N, 7.09 %. Found: C, 66.86; H, 4.87; N, 7.13 %.

4-(3-Aminophenyl)-3-(2,4-dichlorophenoxy)-1-(4-methoxyphenyl)-azetidin-2-one (3d)

White crystal purified by column chromatography (eluent 5:1 $CHCl_3$/EtOAc) (yield 93 %); mp: 142–144 °C; IR

(KBr, cm^{-1}): 1,747 (CO, β-lactam), 3,358, 3,441 (NH_2); ^{1}H-NMR (DMSO) δ (ppm): 3.68 (OMe, s, 3H), 5.03 (NH_2, s, 2H), 5.47 (H-4, d, $J = 4.6$ Hz, 1H), 5.86 (H-3, d, $J = 4.6$ Hz, 1H), 6.39–7.43 (ArH, m, 11H); ^{13}C-NMR δ (ppm); 60.3 (OMe), 65.9 (C-4), 85.8 (C-3), 117.9, 119.2, 119.6, 120.9, 121.3, 123.5, 127.4, 130.7, 132.7, 133.6, 134.3, 135.2, 138.1, 153.5, 156.1, 161.1 (aromatic carbons), 166.4 (CO, β-lactam); GC–MS $m/z = 429$ [M+]; Anal. calcd for $C_{22}H_{18}Cl_2N_2O_3$: C, 61.55; H, 4.23; N, 6.53 %. Found: C, 61.57; H, 4.19; N, 6.56 %.

4-(3-Aminophenyl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (3e)

White powder purified by column chromatography (eluent 5:1 $CHCl_3$/EtOAc) (yield 92 %); mp: 200 °C; IR (KBr, cm^{-1}): 1,739 (CO, β-lactam), 3,359, 3,436 (NH_2); ^{1}H-NMR (DMSO) δ (ppm): 3.68 (OMe, s, 3H), 5.04 (NH_2, s, 2H), 5.45 (H-4, d, $J = 4.7$ Hz, 1H), 5.73 (H-3, d, $J = 4.7$ Hz, 1H), 6.52–7.24 (ArH, m, 13H); ^{13}C-NMR δ (ppm); 55.2 (OMe), 61.3 (C-4), 80.6 (C-3), 112.7, 113.9, 114.4, 115.2, 115.8, 118.3, 121.7, 128.6, 129.2, 130.2, 133.7, 148.4, 155.8, 156.7 (aromatic carbons), 162.2 (CO, β-lactam); GC–MS $m/z = 360$ [M+]; Anal. calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77 %. Found: C, 73.45; H, 5.54; N, 7.80 %.

4-(3-Aminophenyl)-1-(4-methoxyphenyl)-3-(naphthalen-2-yloxy) azetidin-2-one (3f)

Light brown powder purified by column chromatography (eluent 5:1 $CHCl_3$/EtOAc) (yield 83 %); mp: 222–224 °C; IR (KBr, cm^{-1}): 1,745 (CO, β-lactam), 3,359, 3,456 (NH_2); ^{1}H-NMR (DMSO) δ (ppm): 3.68 (OMe, s, 3H), 5.02 (NH_2, s, 2H), 5.55 (H-4, d, $J = 4.4$ Hz, 1H), 5.89 (H-3, d, $J = 4.4$ Hz, 1H), 6.34–7.79 (ArH, m, 15H); ^{13}C-NMR δ (ppm); 60.4 (OMe), 66.5 (C-4), 85.8 (C-3), 114.1, 118.0, 119.2, 119.7, 121.2, 123.2, 123.6, 129.3, 131.7, 131.9, 132.7, 133.8, 134.1, 134.4, 135.5, 138.9, 138.9, 153.6, 159.7, 161.1 (aromatic carbons), 167.3 (CO, β-lactam); GC–MS $m/z = 410$ [M+]; Anal. calcd for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82 %. Found: C, 76.08; H, 5.38; N, 6.85 %.

4-(4-Aminophenyl)-1-(4-chlorophenyl)-3-phenoxyazetidin-2-one (3 g)

White powder purified by column chromatography (eluent 5:1 $CHCl_3$/EtOAc) (yield 62 %); mp: 210–212 °C; IR (KBr, cm^{-1}): 1,745 (CO, β-lactam), 3,301, 3,379 (NH_2); ^{1}H-NMR (DMSO) δ (ppm): 5.08 (NH_2, s, 2H), 5.50 (H-4, d, $J = 4.6$ Hz, 1H), 5.74 (H-3, d, $J = 4.6$ Hz, 1H), 6.38–7.41 (ArH, m, 13H); ^{13}C-NMR δ (ppm); 61.2 (C-4), 80.6 (C-3), 113.4, 115.0, 118.5, 118.7, 121.6, 127.8, 128.9, 129.1, 129.2, 135.6, 148.8, 156.5 (aromatic carbons), 163.1 (CO, β-lactam); GC–MS $m/z = 364$ [M+]; Anal. calcd for $C_{21}H_{17}ClN_2O_2$: C, 69.14; H, 4.70; N, 7.68 %. Found: C, 69.13; H, 4.72; N, 7.64 %.

General procedure for the synthesis of β-lactams 4a–g

β-Lactams **3a**–**g** (0.50 mmol) were dissolved in 10 mL dry CH_2Cl_2, $NaHCO_3$ (0.05 g, 0.06 mmol) was added and the mixture was cooled in an ice bath for 20 min, then acryloyl chloride (0.04 mL, 0.50 mmol) was added and the mixture was stirred at 0 °C for 1 h. The crude product was purified by silica gel chromatography (eluent 4:1 $CHCl_3$/EtOAc) to yield pure β-lactams **4a**–**g**.

N-(4-(1-(4-Methoxyphenyl)-4-oxo-3-phenoxyazetidin-2-yl) phenyl) acrylamide (4a)

White powder purified by thin layer chromatography (eluent 4:1 $CHCl_3$/EtOAc) (yield 72 %); mp: 168 °C; IR (KBr, cm^{-1}): 1,663 (CO, amide), 1,742 (CO, β-lactam), 3,300 (NH); ^{1}H-NMR (DMSO) δ (ppm): 3.66 (OMe, s, 3H), 5.61 (H-4, d, $J = 4.7$ Hz, 1H), 5.67 (vinylic, d, $J = 10.0$ Hz, 1H), 5.78 (H-3, d, $J = 4.7$ Hz, 1H), 6.16 (vinylic, d, $J = 16.8$ Hz, 1H), 6.33 (vinylic, dd, $J = 10.0$, 16.8 Hz, 1H), 6.78–7.54 (ArH, m, 13H), 10.09 (NH, s, 1H); ^{13}C-NMR δ (ppm); 55.1 (OMe), 60.5 (C-4), 80.4 (C-3), 114.4, 114.9, 118.4, 118.9, 121.7, 126.8, 127.9, 128.6, 129.2, 130.0, 131.7, 138.9, 155.8, 156.4 (aromatic and vinylic carbons), 162.0 (CO, β-lactam), 163.0 (CO, amide); GC–MS $m/z = 414$ [M+]; Anal. calcd for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76 %. Found: C, 72.43; H, 5.34; N, 6.76 %.

N-(4-(3-(2,4-Dichlorophenoxy)-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl) phenyl) acrylamide (4b)

White crystal purified by thin layer chromatography (eluent 4:1 $CHCl_3$/EtOAc) (yield 71 %); mp: 192 °C; IR (KBr, cm^{-1}): 1,666 (CO, amide), 1,735 (CO, β-lactam), 3,332 (NH); ^{1}H-NMR (DMSO) δ (ppm): 3.67 (OMe, s, 3H), 5.62 (H-4, d, $J = 4.6$ Hz, 1H), 5.71 (vinylic, d, $J = 9.8$ Hz, 1H), 5.79 (H-3, d, $J = 4.6$ Hz, 1H), 6.15 (vinylic, $J = 16.9$ Hz, d, 1H), 6.31 (vinylic, dd, $J = 9.8$, 16.9 Hz, 1H), 6.79–7.84 (ArH, m, 11H), 10.10 (NH, s, 1H); ^{13}C-NMR δ (ppm); 55.1 (OMe), 60.6 (C-4), 80.4 (C-3), 114.4, 114.9, 118.4, 118.4, 118.9, 121.7, 126.9, 127.9, 128.6, 129.2, 129.2, 130.0, 131.6, 138.9, 155.8, 156.4 (aromatic and vinylic carbons), 162.0 (CO, β-lactam), 163.0 (CO, amide); GC–MS $m/z = 483$ [M+]; Anal. calcd for $C_{25}H_{20}Cl_2N_2O_4$: C, 62.12; H, 4.17; N, 5.80 %. Found: C, 62.10; H, 4.18; N, 5.81 %.

N-(4-(3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl) phenyl) acrylamide (4c)

White powder purified by thin layer chromatography (eluent 4:1 $CHCl_3$/EtOAc) (yield 73 %); mp: 198–200 °C; IR (KBr, cm^{-1}): 1,666 (CO, amide 1,743 (CO, β-lactam)), 3,332 (NH); ^{1}H-NMR (DMSO) δ (ppm): 3.67 (OMe, s, 3H), 5.62 (H-4, d, $J = 4.4$ Hz, 1H), 5.71 (vinylic, d, $J = 9.7$ Hz, 1H), 5.81 (H-3, d, $J = 4.4$ Hz, 1H), 6.18 (vinylic, $J = 17.0$ Hz, d, 1H), 6.26 (vinylic, dd, $J = 9.7$, 17.0 Hz, 1H), 6.82–7.55 (ArH, m, 12H), 10.12 (NH, s, 1H); ^{13}C-NMR δ (ppm); 55.1 (OMe), 60.3 (C-4), 80.4 (C-3), 114.5, 116.7, 118.4, 118.9, 125.4, 126.9, 127.6, 128.6, 129.0, 129.9, 131.6, 138.9, 155.1, 155.9 (aromatic and vinylic carbons), 161.6 (CO, β-lactam), 163.0 (CO, amide); GC–MS *m/z* = 448 [M+]; Anal. calcd for $C_{25}H_{21}ClN_2O_4$: C, 66.89; H, 4.72; N, 6.24 %. Found: C, 66.86; H, 4.70; N, 6.21 %.

N-(3-(3-(2,4-Dichlorophenoxy)-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl) phenyl) acrylamide (4d)

White powder purified by thin layer chromatography (eluent 4:1 $CHCl_3$/EtOAc) (yield 78 %); mp: 166–168 °C; IR (KBr, cm^{-1}): 1,651 (CO, amide), 1,738 (CO, β-lactam), 3,294 (NH); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.66 (OMe, s, 3H), 5.28 (H-4, d, $J = 4.9$ Hz, 1H), 5.41 (H-3, d, $J = 4.9$ Hz, 1H), 5.64 (vinylic, d, $J = 10.1$ Hz, 1H), 6.22 (vinylic, dd, $J = 10.1$, 16.7 Hz, 1H), 6.31 (vinylic, d, $J = 16.7$ Hz, 1H), 6.69–7.60 (ArH, m, 11H), 7.53 (NH, s, 1H); ^{13}C-NMR δ (ppm); 54.4 (OMe), 60.3 (C-4), 80.5 (C-3), 113.4, 113.4, 115.6, 117.8, 117.8, 118.2, 119.3, 123.1, 126.4, 127.0, 128.2, 128.9, 129.0, 130.0, 132.2, 137.1, 150.3, 155.6 (aromatic and vinylic carbons), 160.6 (CO, β-lactam), 162.6 (CO, amide); GC–MS *m/z* = 482 [M+]; Anal. calcd for $C_{25}H_{20}Cl_2N_2O_4$: C, 62.12; H, 4.17; N, 5.80 %. Found: C, 62.13; H, 4.20; N, 5.79 %.

N-(3-(1-(4-Methoxyphenyl)-4-oxo-3-phenoxyazetidin-2-yl) phenyl) acrylamide (4e)

White powder purified by thin layer chromatography (eluent 4:1 $CHCl_3$/EtOAc) (yield 89 %); mp: 160 °C; IR (KBr, cm^{-1}): 1,674 (CO, amide), 1,743 (CO, β-lactam), 3,317 (NH); ^{1}H-NMR (DMSO) δ (ppm): 3.67 (OMe, s, 3H), 5.63 (H-4, d, $J = 4.7$ Hz, 1H), 5.68 (vinylic, d, $J = 9.8$ Hz, 1H), 5.82 (H-3, d, $J = 4.7$ Hz, 1H), 6.23 (vinylic, d, $J = 17.0$ Hz, 1H), 6.39 (vinylic, dd, $J = 9.8$, 17.0 Hz, 1H), 6.79–7.65 (ArH, m, 13H), 10.05 (NH, s, 1H); ^{13}C-NMR δ (ppm); 55.1 (OMe), 60.9 (C-4), 80.5 (C-3), 114.5, 115.1, 118.2, 118.3, 119.1, 121.8, 123.6, 126.9, 128.6, 129.3, 130.0, 131.6, 133.9, 138.9, 155.9, 156.4 (aromatic and vinylic carbons), 162.0 (CO, β-lactam), 163.0 (CO, amide); GC–MS *m/z* = 414 [M+]; Anal. calcd for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76 %. Found: C, 72.40; H, 5.33; N, 6.75 %.

N-(3-(1-(4-Methoxyphenyl)-3-(naphthalene-2-yloxy)-4-oxoazetidin-2-yl) phenyl) acrylamide (4f)

White powder purified by thin layer chromatography (eluent 4:1 $CHCl_3$/EtOAc) (yield 60 %); mp: 190 °C; IR (KBr, cm^{-1}): 1,689 (CO, amide), 1,743 (CO, β-lactam), 3,332 (NH); ^{1}H-NMR (DMSO) δ (ppm): 3.68 (OMe, s, 3H), 5.71 (vinylic, d, $J = 9.9$ Hz, 1H), 5.74 (H-4, d, $J = 4.7$ Hz, 1H), 5.97 (H-3, d, $J = 4.7$ Hz, 1H), 6.17 (vinylic, d, $J = 17.2$ Hz, 1H), 6.25 (vinylic, dd, $J = 9.9$, 17.2 Hz, 1H), 6.90–7.78 (ArH, m, 12H), 10.10 (NH, s, 1H); ^{13}C-NMR δ (ppm); 55.2 (OMe), 60.8 (C-4), 80.5 (C-3), 108.8, 114.5, 117.8, 118.1, 118.4, 119.1, 123.7, 124.1, 126.5, 126.7, 126.9, 127.4, 128.6, 128.9, 129.3, 130.0, 131.6, 133.5, 133.9, 138.9, 154.1, 155.9 (aromatic and vinylic carbons), 161.9 (CO, β-lactam), 163.0 (CO, amide); GC–MS *m/z* = 464 [M+]; Anal. calcd for $C_{29}H_{24}N_2O_4$: C, 74.98; H, 5.21; N, 6.03 %. Found: C, 74.97; H, 5.18; N, 6.04 %.

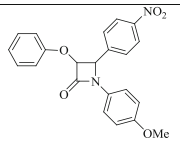
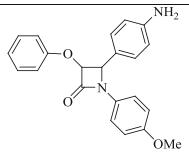
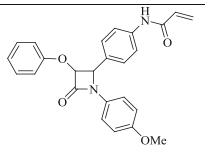
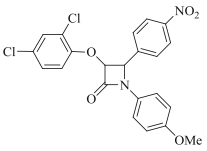
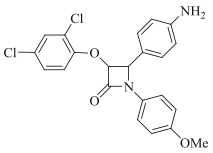
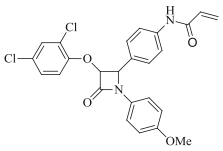
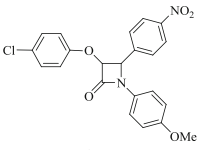
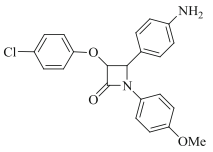
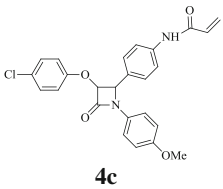
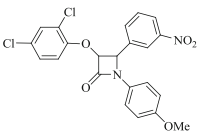
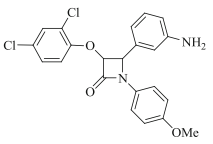
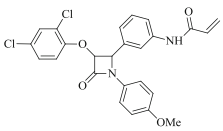
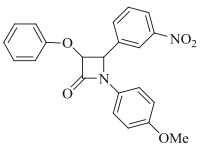
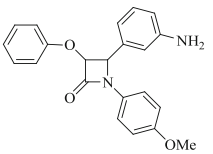
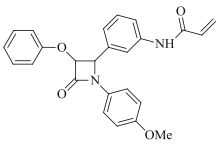
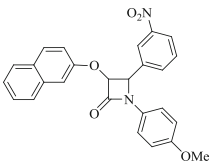
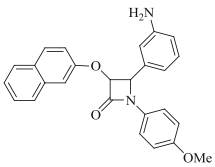
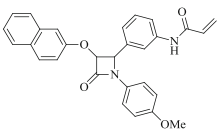
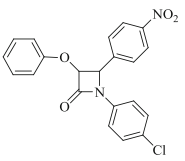
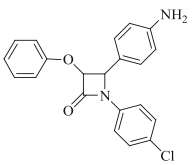
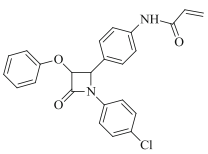
N-(4-(1-(4-Chlorophenyl)-4-oxo-3-phenoxyazetidin-2-yl) phenyl) acrylamide (4 g)

White powder purified by thin layer chromatography (eluent 4:1 $CHCl_3$/EtOAc) (yield 56 %); mp: 228 °C; IR (KBr, cm^{-1}): 1,666 (CO, amide), 1,738 (CO, β-lactam), 3,317 (NH); ^{1}H-NMR (DMSO) δ (ppm): 5.68 (H-4, d, $J = 4.7$ Hz, 1H), 5.73 (vinylic, d, $J = 9.8$ Hz, 1H), 5.84 (H-3, d, $J = 4.7$ Hz, 1H), 6.13 (vinylic, d, $J = 17.0$ Hz, 1H), 6.33 (vinylic, dd, $J = 9.8$, 17.0 Hz, 1H), 6.79–7.89 (ArH, m, 13H), 10.11 (NH, s, 1H); ^{13}C-NMR δ (ppm); 60.7 (C-4), 80.6 (C-3), 114.9, 118.7, 118.9, 121.8, 126.9, 127.4, 128.0, 128.6, 129.2, 129.3, 131.6, 135.4, 139.0, 156.3 (aromatic and vinylic carbons), 162.8 (CO, β-lactam), 163.0 (CO, amide); GC–MS *m/z* = 418 [M+]; Anal. calcd for $C_{24}H_{19}ClN_2O_3$: C, 68.82; H, 4.57; N, 6.69 %. Found: C, 68.80; H, 4.58; N, 6.69 %.

Preparation of the polyacrylate nanoparticle emulsions

Poly(butyl acrylate-styrene) nanoparticles were prepared by emulsion polymerization. β-Lactams **4a**, **4c** or **4d** (30 mg, 3 % wt/wt) were dissolved in a 7:3 (wt/wt) mixture of butyl acrylate (108.5 mg), styrene (46.5 mg) at 70 °C and heated for 10 min under Ar atmosphere. Deionized water (8.0 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

Table 1 Structure of monocyclics β-lactams **2a–g**, **3a–g**, and **4a–g**

Entry	Structures of **2a-g**	Yield (%) [a]	Structures of **3a-g**	Yield (%) [a]	Structures of **4a-g**	Yield (%) [a]
1	 **2a**	64	 **3a**	63	 **4a**	72
2	 **2b**	61	 **3b**	67	 **4b**	71
3	 **2c**	66	 **3c**	63	 **4c**	73
4	 **2d**	53	 **3d**	93	 **4d**	78
5	 **2e**	47	 **3e**	92	 **4e**	89
6	 **2f**	72	 **3f**	83	 **4f**	60
7	 **2g**	51	 **3g**	62	 **4g**	56

[a] Isolated yields

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 (0.2 μm).

Analysis of the emulsions of 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, then the grid was viewed on the microscope.

Results and discussion

The Staudinger reaction ([2 + 2] ketene–imine cycloaddition reaction) is one of the most common methods for the synthesis of monocyclic 2-azetidinones [18]. Cycloaddition reactions of imines **1a–g** with different substituted acetic acids in the presence of *p*-toluenesulfonyl chloride and triethylamine afforded *cis* 2-azetidinones **2a–g** in moderate to good yields (Scheme 1; Table 1). The *cis* stereochemistry of these β-lactams was confirmed from the coupling constant of H-3 and H-4, which was calculated to be $J_{3,4} = 4.3–5.1$ Hz for the *cis* stereoisomers.

The X-ray crystallography of **2e** [19] (Fig. 1) showed that the β-lactam ring (N1/C8–C10) is nearly planar, with a maximum deviation of 0.023 (2) Å for N1. Its mean plane makes dihedral angles of 11.61 (19), 74.5 (2), and 72.3 (2)°, respectively, with three aromatic rings (C1–C6), (C11–C16), and (C17–C22). A weak intramolecular C–H···O hydrogen bond contributes to the stability of the molecular configuration. The crystal structure is stabilized by intermolecular C–H···O hydrogen-bonding and C–H···π stacking interactions. Furthermore, a π–π interaction helps to stabilize the crystal structure.

Then β-lactams **2a–g** containing the nitro group at para or meta position of the phenyl ring on C-4 of 2-azetidinone were reduced easily to aminophenyl β-lactams **3a–g** by Raney Ni and hydrazine hydrate in EtOH/H_2O (9:1) in good to excellent yields (Scheme 1; Table 1). In the presence of Raney nickel, hydrazine hydrate decomposed to nitrogen, hydrogen and ammonia [20] but in this condition β-lactam ring has not been affected by hydrazine or ammonia.

Then aminophenyl β-lactams **3a–g** were dissolved in CH_2Cl_2 and in the presence of acryloyl chloride and $NaHCO_3$ as basic catalysts were converted to β-lactam monomers **4a–g** in moderate to good yields (Scheme 1; Table 1).

Preparation of emulsified polyacrylate nanoparticles as antibacterial drug carriers have been investigated [6, 7, 16]. These nanopolymeric emulsions can be prepared easily in water by radical-induced emulsion polymerization using an acrylated derivative of the β-lactam as a comonomer in a warmed mixture of butyl acrylate and styrene. For this, the solubility of acrylated β-lactam monomers **4a–g** was examined in a 7:3 (w:w) mixture of butyl acrylate and styrene. It was found that β-lactam monomers **4a**, **4c,** and **4d** were readily dissolved to homogeneity in the mixture of butyl acrylate and styrene at 70 °C under Ar atmosphere. The mixture was then pre-emulsified in deionized water and sodium dodecyl sulfate (SDS) (1 weight %) as surfactant. After about 30 min, the homogenous solution was treated with potassium persulfate (0.5 weight %) to start free radical polymerization for 7 h (Scheme 1).

Then the nanopolymeric emulsions were purified by continuous extraction using ethyl acetate followed by centrifugation on a bench top centrifuge, to remove minor impurities, such as excess surfactant or residual monomers without altering the physical characteristics of the

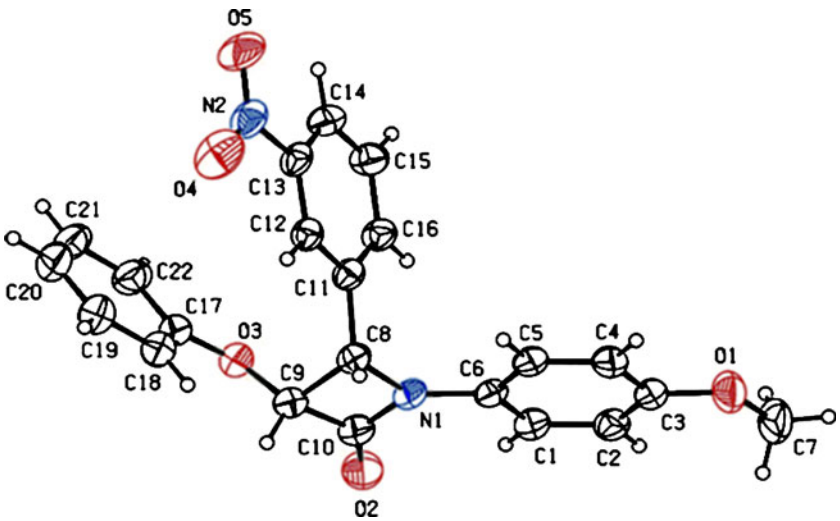
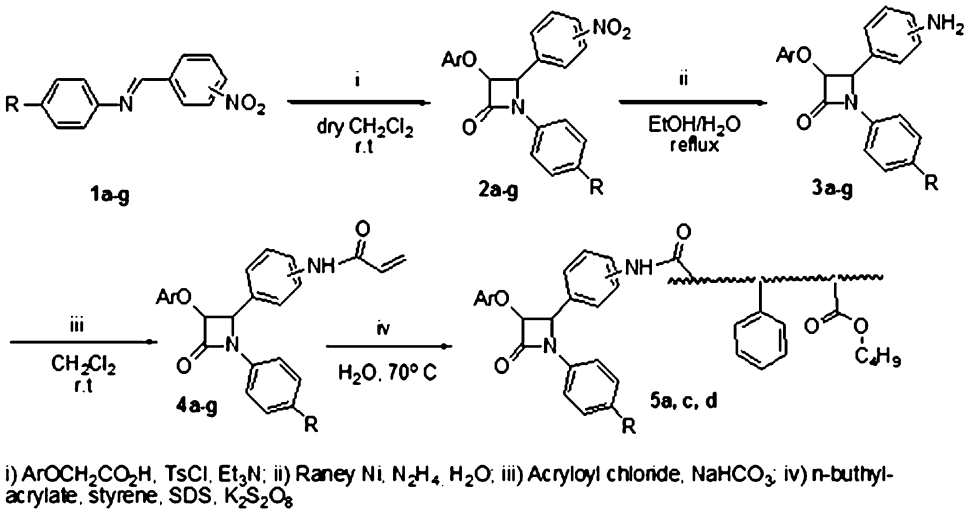


Fig. 1 X-ray crystal structure of **2e**

Scheme 1 Synthesis of monocyclic β-lactams and nano-β-lactams



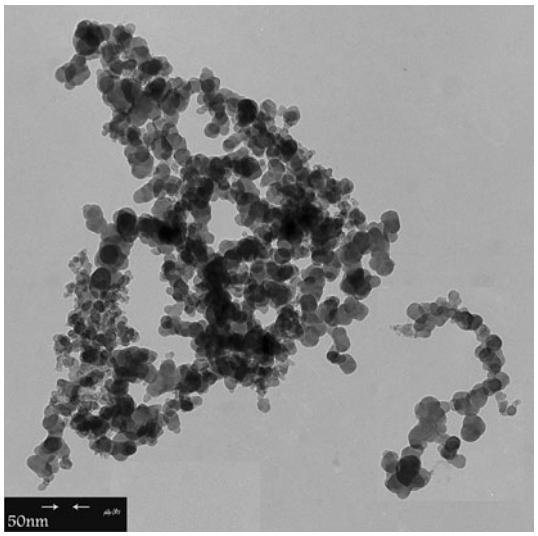


Fig. 2 TEM image of **5c**

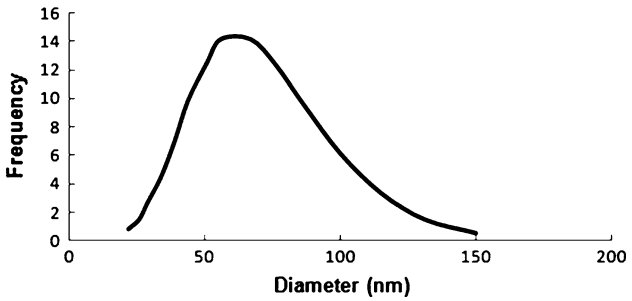


Fig. 3 DLS of **5c**

nanoparticles in the emulsion [21]. Then the samples were filtered with cellulose acetate membrane (0.2 μm) to remove any large scale particles.

The morphology and the particle size analysis of the emulsions were performed by TEM and DLS. TEM image of **5c** is shown in Fig. 2, and as it is seen in the image, the nanoparticles were essentially perfectly spherical, which was similar to the size distribution profile obtained by DLS analysis (Fig. 3). DLS analysis of the final emulsion showed that the average diameter of the **5a**, **5c**, and **5d** is uniformly about 56.6, 62, and 66.9 nm, respectively, with size distributions spanning from about 20–150 nm.

Conclusions

In this study, several polyacrylate nano β-lactams have been synthesized from the corresponding monomeric β-lactams by emulsion polymerization. The polyacrylated β-lactam nanoparticles showed average diameter of 50–70 nm.

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

References

1. N.S. Vatmurge, B.G. Hazra, V.S. Pore, F. Shirazi, P.S. Chavan, M.V. Deshpande, Bioorg. Med. Chem. Lett. **18**, 2043 (2008)
2. R.J. Shah, N.R. Modi, M.J. Patel, L.J. Patel, B.F. Chauhan, M.M. Patel, Med. Chem. Res. **20**, 587 (2011)
3. P.D. Mehta, N.P.S. Sengar, A.K. Pathak, Eur. J. Med. Chem. **45**, 5541 (2010)
4. S.S.B. Reshma, A. Bhalla, G. Hundal, Tetrahedron **65**, 10060 (2009)
5. S.J. Douglas, S.S. Davis, L. Illum, Int. J. Pharm. **34**, 145 (1986)
6. E. Turos, J.-Y. Shim, Y. Wang, K. Greenhalgh, G.S.K. Reddy, S. Dickey, D.V. Lim, Bioorg. Med. Chem. Lett. **17**, 53 (2007)
7. J.C. Garay-Jimenez, D. Gergeres, A. Young, D.V. Lim, E. Turos, Nanomedcine: NBM **5**, 443 (2009)
8. A.L.Z. Lee, S. Venkataraman, S.B.M. Sirat, S. Gao, J.L. Hedrick, Y.Y. Yang, Biomaterials **33**, 1921 (2012)
9. A. Mahmud, X.-B. Xiong, A. Lavasanifar, Eur. J. Pharm. Biopharm. **69**, 923 (2008)

10. K.N. Kontogiannopoulos, A.N. Assimopoulou, S. Hatziantoniou, K. Karatasos, C. Demetzos, V.P. Papageorgiou, Int. J. Pharm. **422**, 381 (2012)
11. S.H. Michelland, M.J. Alonso, A. Andremont, P. Maincen, J. Sauzieres, P. Couvreur, Int. J. Pharm. **35**, 121 (1987)
12. G. Fontana, G. Pitarresi, V. Tomarchio, B. Carlisi, P.L. San Biagio, Biomaterials **19**, 1009 (1998)
13. G. Fontana, M. Licciardi, S. Mansueto, D. Schillaci, G. Giammona, Biomaterials **22**, 2857 (2001)
14. N.S. Santos-Magalhaes, A. Pontes, V.M.W. Pereira, M.N.P. Caetano, Int. J. Pharm. **208**, 71 (2000)
15. S.C. Abeylath, E. Turos, Carbohydr. Polym. **70**, 32 (2007)
16. J.C. Garay-Jimenez, E. Turos, Bioorg. Med. Chem. Lett. **21**, 4589 (2011)
17. E. Turos, G.S.K. Reddy, K. Greenhalgh, P. Ramaraju, S.C. Abeylath, S. Jang, S. Dickeyc, D.V. Lim, Bioorg. Med. Chem. Lett. **17**, 3468 (2007)
18. G.I. Georg, P. He, J. Kant, J. Mudd, Tetrahedron Lett. **31**, 451 (1990)
19. Z. Baktır, M. Akkurt, A. Jarrahpour, R. Heiran, Acta Cryst. **E67**, o537 (2011)
20. N.R. Ayyangar, A.G. Lugade, P.V. Nikrad, V.K. Sharma, Synthesis **11**, 640 (1981)
21. J. Garay-Jimenez, A. Young, D. Gergeres, K. Greenhalgh, E. Turos, Nanomedicine: NBM **4**, 98 (2008)