Advances in Nanochemistry
ISSN: 2676-5462

Research

Decoration of monocyclic β-lactams with silver nanoparticles

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Received 16th July 2021,
Accepted 28th August 2021,
DOI: 10.22126/anc.2021.6699.1029

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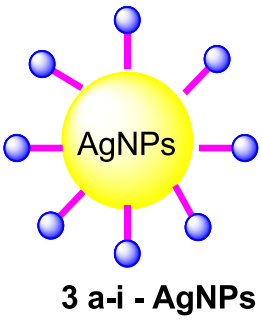
Abstract

Some monocyclic β-lactams bearing the amino moiety have been synthesized from β-lactams with a nitro functional group. First of all, the nitro β-lactams (2a-f) were prepared via Staudinger reactions of the corresponding imines with different substituted acetic acids. Then, to have more electron-rich sites which can bind to the electron-deficient silver nanoparticles (AgNPs), they converted to amino β-lactams (3a-f) bearing NH_2 group by a reduction process. The cycloadducts were characterized by spectral data, including ^{1}H-NMR, ^{13}C-NMR, IR, mass spectroscopy, elemental analyses, and X-ray crystallography. As the last step, the combination of those amino β-lactams with AgNPs was simply obtained by treatment of them with pre-prepared AgNPs solution. SEM images of β-lactams-AgNPs showed nanoparticles distributed on the surface, and UV–Vis absorption spectra of β-lactams-AgNPs displayed a broad peak in the range of 400-550 nm. These observations confirmed the presence of AgNPs on the surface.



Keywords: *Silver nanoparticles (AgNPs), 2-Azetidinone, UV-Vis spectroscopy, SEM image.*

Introduction

Scientists have been very interested in β-lactam compounds since the 1940s, when the antibiotic properties of the first semisynthetic penicillins were discovered. In the late 1970s and early 1980s, several monocyclic β-lactams such as nocardicins and monobactams with high antibacterial activity have been discovered in nature. In view of this, the biological activity of β-lactams is absolutely correlated to functional groups on the 2-azetidinone ring[1] and does not require a bicyclic structure to have antibacterial properties.[2] In addition well-known antimicrobial properties of β-lactam, they have been shown other interesting biological activities such as antimalarial,[3,4] antifungal,[5] anticancer,[6] antidiabetic,[7] anti-HIV,[8] and anti-inflammatory[9,10] activities. However, the empirical therapy and broad use of this group of drugs have been caused bacterial resistance. Therefore, some methods have been developed for overcoming this phenomenon. One was the modification of the structure of known active compounds;[11] another approach was to use dual-action cephems, so if bacteria have resistance to one of them, the other one will kill them.[12]

Recently, medical scientists have shown much interest in nanosized organic and inorganic particles due to their high reactivity to biological functionalization.[13,14] For centuries, silver-based compounds have been used in traditional medicines to treat various infections. Silver nanoparticles (AgNPs), as one of the most interesting nanoparticles, possess well-developed surface chemistry, chemical stability, and appropriate size.[15] Different research group studied antimicrobial,[15-18] antiviral,[19,20] anti-inflammatory,[18,21] and anticancer[18] activities of AgNPs. Several researchers have synthesized AgNPs combined with some antibiotics,[22-24] methylcellulose,[25] gelatin,[26] chitosan,[27] and catechol-conjugated chitosan,[28] as well as investigated of their antimicrobial activity. The incorporation of nanosilver into antibiotics has a synergistic antibacterial efficiency. Therefore, our interest in β-lactam chemistry led us to study the combination of some amino β-lactams with AgNPs.

Experimental

General

All required chemicals and solvents were provided from the Fluka, Merck, and Acros chemical companies. The delivered CH_2Cl_2 and Et_3N were dried using distillation over CaH_2 and stored over 4 A° molecular sieves. The 1H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 using a Bruker Avance DPX instrument (operating at 250 and 62.9 MHz for ^{1}H and ^{13}C, respectively). Chemical shifts were reported in ppm (δ) downfield from TMS. All the coupling constants (*J*) are in Hertz. IR spectra were recorded using a Shimadzu FT-IR 8300 spectrophotometer. The mass spectra were provided by a Shimadzu GC–MS QP 1000 EX instrument.

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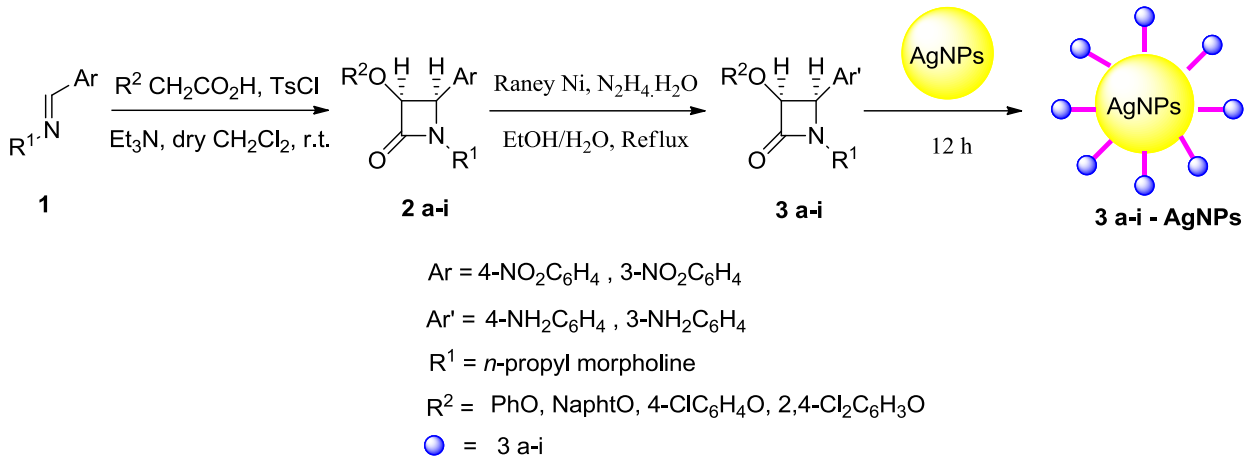
Cite this article: Heiran, R. and Jarrahpour, A. (2021). Decoration of monocyclic β-lactams with silver nanoparticle. *Advances in Nanochemistry*, 3(1), 34-39. DOI: 10.22126/anc.2021.6699.1029

Publisher: Razi University



Scheme 1. *The synthetic route to amino β-lactams –AgNPs.*

Elemental analyses were obtained by 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. Scanning electron microscope (SEM) images were obtained by Hitachi S-4160 field emission SEM (FESEM) at accelerating voltages of 30 kV. HORIBA dynamic light scattering (DLS) instrument was used to check nanoparticles size distribution. Thin layer chromatography (TLC) was used to monitor the progress of the reaction by silica gel 254 analytical sheets and the products purification was achieved by silica gel column chromatography (Merck Kieselgel 230–270 mesh).

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

A mixture of Schiff base **(1)** (5.00 mmol), triethylamine (25.00 mmol), acetic acid derivative (7.5 mmol), and *p*-toluenesulfonyl chloride (7.5 mmol) in dry CH_2Cl_2 (25 mL) was stirred at room temperature overnight. After completion of the reaction (checked by TLC monitoring), the mixture was washed with HCl (1 N), saturated $NaHCO_3$ solution, brine, dried (Na_2SO_4), and then solvent was evaporated under vacuum to afford the crude β-lactams **2a–f**. Finally, the desired products were purified by gel column chromatography (eluent 10:1 EtOAc/EtOH).[9]

1-(3-Morpholinopropyl)-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one ***(2a)***

Off-white crystalline solid (yield 76 %). mp 153-155 °C. IR (KBr, cm^{-1}) 1751 (CO, *β*-lactam), 1350, 1520 (NO_2). ^{1}H-NMR ($CDCl_3$) δ 1.65 (aliphatic chain, m, 2H), 2.31 (aliphatic chain and morpholine ring, m, 6H), 2.97 (aliphatic chain, m, 1H), 3.52 (aliphatic chain and morpholine ring, m, 5H), 5.05 (H-4, d, *J* = 4.5 Hz, 1H), 5.48 (H-3, d, *J* = 4.5 Hz, 1H), 6.67 (ArH, d, *J* = 8.7 Hz, 2H), 6.83 (ArH, t, *J* = 7.7 Hz, 1H), 7.07 (ArH, t, *J* = 7.7 Hz, 2H), 7.48 (ArH, d, *J* = 8.7 Hz, 2H), 8.11 (ArH, d, *J* = 8.7 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ 24.4 (aliphatic chain), 39.2 (aliphatic chain), 53.6 (morpholine ring), 56.0 (aliphatic chain), 61.5 (C-4), 66.8 (morpholine ring), 81.9 (C-3), 115.2, 122.4, 123.4, 129.3, 129.4, 141.0, 148.1, 156.4 (aromatic carbons), 165.5 (CO, *β*-lactam). MS m/z = 411[M^+]. Anal. Calcd. for $C_{22}H_{25}N_3O_5$: C, 64.22; H, 6.12; N, 10.21%. Found: C, 64.40; H, 6.25; N, 10.17 %.

3-(4-Chlorophenoxy)-1-(3-morpholinopropyl)-4-(4-nitrophenyl) azetidin-2-one ***(2b)***

Pea green solid (yield 74 %). mp 108-110 °C. IR (KBr, cm^{-1}) 1751 (CO, *β*-lactam), 1350, 1520 (NO_2). ^{1}H-NMR ($CDCl_3$) δ 1.68 (aliphatic chain, m, 2H), 2.31 (aliphatic chain and morpholine ring, m, 6H), 3.00 (aliphatic chain, m, 1H), 3.54 (aliphatic chain and morpholine ring, m, 5H), 5.04 (H-4, d, *J* = 4.5 Hz, 1H), 5.42 (H-3, d, *J* = 4.5 Hz, 1H), 6.66 (ArH, d, *J* = 8.6 Hz, 2H), 7.07 (ArH, d, *J* = 8.5 Hz, 2H), 7.49 (ArH, d, *J* = 8.6 Hz, 2H), 8.16 (ArH, d, *J* = 8.5 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ 24.4 (aliphatic chain), 39.2 (aliphatic chain), 53.6 (morpholine ring), 56.0 (aliphatic chain), 61.3 (C-4), 66.8 (morpholine ring), 82.0 (C-3), 116.6, 123.6, 127.5, 129.3, 129.4, 140.7, 148.2, 155.0 (aromatic carbons), 165.2 (CO, *β*-lactam). MS m/z = 443 [M^+]. Anal. Calcd. for $C_{22}H_{24}ClN_3O_5$: C, 59.26; H, 5.43; N, 9.42%. Found: C, 59.32; H, 5.49; N, 9.39 %.

3-(2,4-Dichlorophenoxy)-1-(3-morpholinopropyl)-4-(4-nitro phenyl) azetidin-2-one ***(2c)***

White solid (yield 63 %). mp 114-116 °C. IR (KBr, cm^{-1}) 1743 (CO, *β*-lactam), 1350, 1520 (NO_2). ^{1}H-NMR ($CDCl_3$) δ 1.62 (aliphatic chain, m, 2H), 2.25 (aliphatic chain and morpholine ring, m, 6H), 2.97 (aliphatic chain, m, 1H), 3.50 (aliphatic chain and morpholine ring, m, 5H), 5.02 (H-4, d, *J* = 4.8 Hz, 1H), 5.37 (H-3, d, *J* = 4.8 Hz, 1H), 6.96 (ArH, d, *J* = 8.7 Hz, 1H), 7.02 (ArH, d, *J* = 8.7 Hz, 1H), 7.13 (ArH, s, 1H), 7.48 (ArH, d, *J* = 8.7 Hz, 2H), 8.15 (ArH, d, *J* = 8.7 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ 24.4 (aliphatic chain), 39.3 (aliphatic chain), 53.6 (morpholine ring), 56.0 (aliphatic chain), 60.9 (C-4), 66.8 (morpholine ring), 82.5 (C-3), 116.4, 123.6, 123.9, 127.6, 127.8, 129.4, 130.1, 140.6, 148.3, 151.2 (aromatic carbons), 164.9 (CO, *β*-lactam). MS m/z = 480 [M^+]. Anal. Calcd. for $C_{22}H_{23}Cl_2N_3O_5$: C, 55.01; H, 4.83; N, 8.75%. Found: C, 55.15; H, 4.97; N, 8.71 %.

1-(3-Morpholinopropyl)-3-(naphthalen-2-yloxy)-4-(4-nitro phenyl) azetidin-2-one ***(2d)***

Pea green solid (yield 79 %). mp 133-135 °C. IR (KBr, cm^{-1}) 1751 (CO, *β*-lactam), 1350, 1520 (NO_2). ^{1}H-NMR ($CDCl_3$) δ 1.69 (aliphatic chain, m, 2H), 2.29 (aliphatic chain and morpholine ring, m, 6H), 3.00 (aliphatic chain, 1H, m), 3.57 (aliphatic chain and morpholine ring, 5H, m), 5.15 (H-4, d, *J* = 4.4 Hz, 1H), 5.64 (H-3, d, *J* = 4.4 Hz, 1H), 6.84 (ArH, d, *J* = 8.9 Hz, 1H), 7.06 (ArH, s, 1H), 6.26-7.69 (ArH, m, 7H), 8.10 (ArH, d, *J* = 8.7 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ 24.5 (aliphatic chain), 39.2 (aliphatic chain), 53.6 (morpholine ring), 56.0 (aliphatic chain 61.5 (C-4), 66.8 (morpholine ring), 81.9 (C-3), 108.7, 118.0, 123.5, 124.4, 126.6, 126.8, 127.7, 129.3, 129.6, 129.7, 133.8, 140.9, 148.1, 154.3 (aromatic carbons), 165.4 (CO, *β*-lactam). MS m/z = 461 [M^+]; Anal. Calcd. for $C_{26}H_{27}N_3O_5$: C, 67.66; H, 5.90; N, 9.10 %. Found: C, 67.54; H, 6.02; N, 9.13 %.

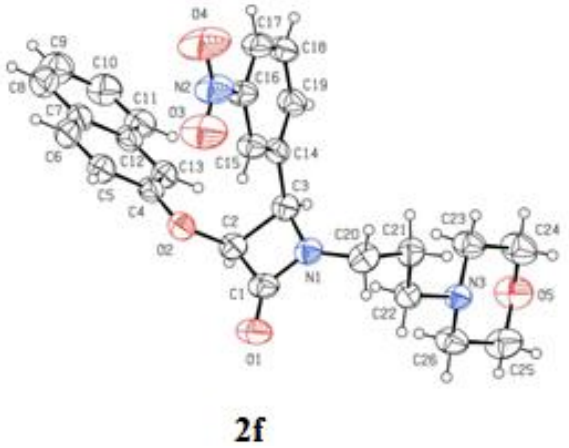


Figure 1. *X-ray crystal structures of compound* ***2f****.*

1-(3-Morpholinopropyl)-4-(3-nitrophenyl)-3-phenoxyazetidin-2-one ***(2e)***

White solid (yield 69 %). mp 101-103 °C. IR (KBr, cm^{-1}) 1751 (CO, *β*-lactam), 1350, 1527 (NO_2). ^{1}H-NMR ($CDCl_3$) δ 1.64 (aliphatic chain, m, 2H), 2.28 (aliphatic chain and morpholine ring, m, 6H), 2.97 (aliphatic chain, m, 1H), 3.51 (aliphatic chain and morpholine ring, m, 5H), 5.00 (H-4, d, *J* = 4.4 Hz, 1H), 5.43 (H-3, d, *J* = 4.4 Hz, 1H), 6.62 (ArH, d, *J* = 7.9 Hz, 2H), 6.81 (ArH, t, *J* = 7.5 Hz, 1H), 7.02 (ArH, t, *J* = 7.9 Hz, 2H), 7.40 (ArH, t, 1H), 7.62 (ArH, d, *J* = 7.8 Hz, 1H), 8.05 (ArH, d, *J* = 8.1 Hz, 1H), 8.12 (ArH, s, 1H). ^{13}C-NMR ($CDCl_3$) δ 24.4 (aliphatic chain), 39.1 (aliphatic chain), 53.6 (morpholine ring), 56.0 (aliphatic chain), 61.5 (C-4), 66.7 (morpholine ring), 81.7 (C-3), 115.2, 122.4, 123.5, 123.8, 129.3, 129.4, 134.3, 135.8, 148.1, 156.3 (aromatic carbons), 165.5 (CO, *β*-lactam). MS m/z = 411[M^+]. Anal. Calcd. for $C_{22}H_{25}N_3O_5$: C, 64.22; H, 6.12; N, 10.21%. Found: C, 64.37; H, 6.20; N, 10.16 %.

1-(3-Morpholinopropyl)-3-(naphthalen—2-yloxy)-4-(3-nitro phenyl) azetidin-2-one ***(2f)***

Off white crystals (yield 63 %). mp: 126-128 °C. IR (KBr, cm^{-1}): 1759 (CO, *β* -lactam), 1350, 1527 (NO_2). ^{1}H-NMR ($CDCl_3$) δ.64 (H-3, d, *J* = 4.4 Hz, 1H), 6.88 (ArH, d, *J* = 8.9 Hz, 1H), 7.07 (ArH, s, 1H), 7.31-8.24 (ArH, m, 7H), 8.23 (ArH, d, *J* = 8.7 Hz, 1H), 8.57 (ArH, s, 1H). ^{13}C-NMR ($CDCl_3$) δ 24.4 (aliphatic chain), 39.2 (aliphatic chain), 53.5 (morpholine ring), 56.0 (aliphatic chain), 61.4 (C-4), 66.7 (morpholine ring), 81.7 (C-3), 108.8, 117.9, 123.4, 123.8, 124.4, 126.6, 126, 127.6, 129.3, 129.5, 129.7, 133.8, 134.4, 135.8, 148.1, 154.2 (aromatic carbons), 165.5 (CO, *β*-lactam). MS m/z = 461 [M^+]. Anal. Calcd. for $C_{26}H_{27}N_3O_5$: C, 67.66; H, 5.90; N, 9.10 %. Found: C, 67.74; H, 6.02; N, 9.13 %.

General Procedure for the synthesis of monocyclic β-lactams ***3a–f***

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

4-(4-Aminophenyl)-1-(3-morpholinopropyl)-3-phenoxyazetidin-2-one ***(3a)***

White solid (yield 96 %). mp 136-138 °C. IR (KBr, cm^{-1}) 1751 (CO, β-lactam), 3356, 3456 (NH_2). ^{1}H-NMR ($CDCl_3$) δ 1.62 (aliphatic chain, m, 2H), 2.29 (aliphatic chain and morpholine ring, m, 6H), 2.95 (aliphatic chain, m, 1H), 3.43 (aliphatic chain, m, 1H), 3.65 (morpholine ring and NH_2, m, 6H), 4.81 (H-4, d, *J* = 4.3 Hz, 1H), 5.34 (H-3, d, *J* = 4.3 Hz, 1H), 6.55 (ArH, d, *J* = 8.4 Hz, 2H), 6.72 (ArH, d, *J* = 8.4 Hz, 2H), 6.83 (ArH, t, *J* = 7.3 Hz, 1H), 7.08 (ArH, d, *J* = 8.3 Hz, 2H), 7.14 (ArH, t, *J* = 8.6 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ 24.4 (aliphatic chain), 38.4 (aliphatic chain), 53.6 (morpholine ring), 56.2 (aliphatic chain),

Table 1. *Structures of monocyclic β-lactams* ***2a-f, 3a-f****.*

Entry	Ar	Ar'	R^1	R^2	Yield (%)
2a	4-$NO_2C_6H_4$	----------	*n*-propyl morpholine	C_6H_5O	76
2b	4-$NO_2C_6H_4$	----------	*n*-propyl morpholine	4-ClC_6H_4O	74
2c	4-$NO_2C_6H_4$	----------	*n*-propyl morpholine	2,4-$Cl_2C_6H_3O$	63
2d	4-$NO_2C_6H_4$	----------	*n*-propyl morpholine	2-naphtyloxy	79
2e	3-$NO_2C_6H_4$	----------	*n*-propyl morpholine	C_6H_5O	69
2f	3-$NO_2C_6H_4$	----------	*n*-propyl morpholine	2-naphtyloxy	63
3a	----------	4-$NH_2C_6H_4$	*n*-propyl morpholine	C_6H_5O	96
3b	----------	4-$NH_2C_6H_4$	*n*-propyl morpholine	4-ClC_6H_4O	92
3c	----------	4-$NH_2C_6H_4$	*n*-propyl morpholine	2,4-$Cl_2C_6H_3O$	67
3d	----------	4-$NH_2C_6H_4$	*n*-propyl morpholine	2-naphtyloxy	79
3e	----------	3-$NH_2C_6H_4$	*n*-propyl morpholine	C_6H_5O	68
3f	----------	3-$NH_2C_6H_4$	*n*-propyl morpholine	2-naphtyloxy	59

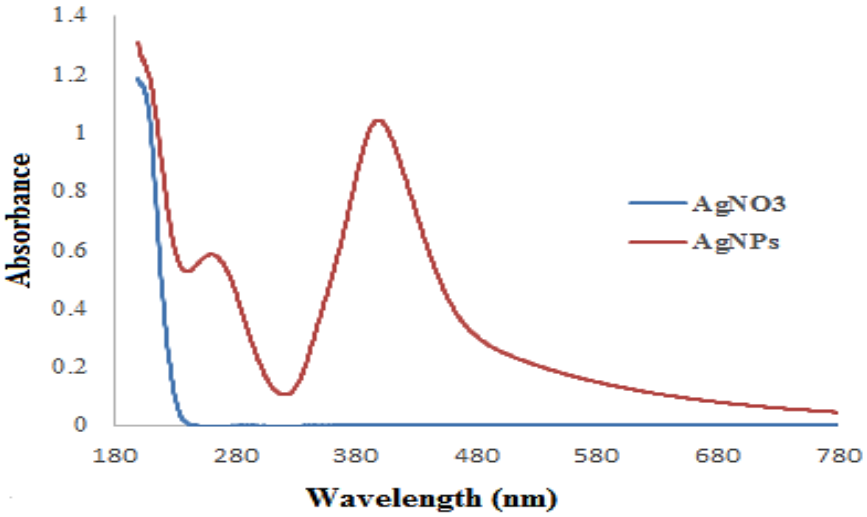


Figure 2. *The UV-Vis absorption spectra of $AgNO_3$ and AgNPs.*

62.2 (C-4), 66.9 (morpholine ring), 81.9 (C-3), 114.7, 115.6, 121.8, 122.2, 129.1, 129.8, 146.9, 157.0 (aromatic carbons), 166.1 (CO, *β*-lactam). MS m/z = 382 [M^+]. Anal. Calcd. for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02 %. Found: C, 69.35; H, 7.15; N, 10.95 %.

4-(4-Aminophenyl)-3-(4-chlorophenoxy)-1-(3-morpholinopropyl) azetidin-2-one ***(3b)***

White solid (yield 92 %). mp 177-180 °C. IR (KBr, cm^{-1}) 1735 (CO, *β*-lactam), 3332, 3409 (NH_2). ^{1}H-NMR ($CDCl_3$) δ 1.56 (aliphatic chain, m, 2H), 2.23 (aliphatic chain and morpholine ring, m, 6H), 2.89 (aliphatic chain, m, 1H), 3.36 (aliphatic chain, m, 1H), 3.59 (morpholine ring and NH_2, m, 6H), 4.74 (H-4, d, *J* = 4.3 Hz, 1H), 5.23 (H-3, d, *J* = 4.3 Hz, 1H), 6.50 (ArH, d, *J* = 8.4 Hz, 2H), 6.59 (ArH, d, *J* = 9.0 Hz, 2H), 6.97 (ArH, d, *J* = 8.4 Hz, 2H), 6.99 (ArH, d, *J* = 9.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ 24.4 (aliphatic chain), 38.5 (aliphatic chain), 53.6 (morpholine ring), 56.2 (aliphatic chain), 62.0 (C-4), 66.9 (morpholine ring), 81.9 (C-3), 114.7, 116.8, 121.9, 126.8, 129.1, 129.8, 147.0, 155.6 (aromatic carbons), 165.7 (CO, *β*-lactam). MS m/z = 416 [M^+]. Anal. Calcd. for $C_{22}H_{26}ClN_3O_3$: C, 63.53; H, 6.30; N, 10.10%. Found: C, 63.67; H, 6.41; N, 10.06 %.

4-(4-Aminophenyl)-3-(2,4-dichlorophenoxy)-1-(3-morpholino propyl)azetidin-2-one ***(3c)***

White solid (yield 67 %). mp 132-134 °C. IR (KBr, cm^{-1}) 1743 (CO, *β*-lactam), 3332, 3409 (NH_2). ^{1}H-NMR ($CDCl_3$) δ 1.63 (aliphatic chain, m, 2H), 2.29 (aliphatic chain and morpholine ring, m, 6H), 2.94 (aliphatic chain, m, 1H), 3.34 (aliphatic chain, m, 1H), 3.62 (morpholine ring and NH_2, m, 6H), 4.79 (H-4, d, *J* = 4.4 Hz, 1H), 5.28 (H-3, d, *J* = 4.4 Hz, 1H), 6.52 (ArH, d, *J* = 8.2 Hz, 2H), 6.74 (ArH, d, *J* = 8.8 Hz, 1H), 6.95 (ArH, d, *J* = 8.8 Hz, 1H), 7.03(ArH, d, *J* = 8.2 Hz, 2H), 7.13 (ArH, s, 1H). ^{13}C-NMR ($CDCl_3$) δ 24.1 (aliphatic chain), 38.4 (aliphatic chain), 53.4 (morpholine ring), 56.0 (aliphatic chain), 61.6 (C-4), 66.5 (morpholine ring), 82.1 (C-3), 114.7, 115.9, 121.5, 123.9, 126.9, 127.2, 129.4, 129.9, 147.2, 151.4 (aromatic carbons), 165.3 (CO, *β*-lactam). MS m/z = 450 [M^+]. Anal. Calcd. for $C_{22}H_{25}Cl_2N_3O_3$: C, 58.67; H, 5.60; N, 9.33%. Found: C, 58.72; H, 5.73; N, 9.37%.

4-(4-Aminophenyl)-1-(3-morpholinopropyl)-3-(naphthalene-2-yloxy)azetidin-2-one ***(3d)***

White solid (yield 79 %). mp 152-154 °C. IR (KBr, cm^{-1}) 1737 (CO, *β*-lactam), 3338, 3430 (NH_2). ^{1}H-NMR ($CDCl_3$) δ 1.71 (aliphatic chain, m, 2H), 2.42 (aliphatic chain and morpholine ring, m, 6H), 2.99 (aliphatic chain, m, 1H), 3.46 (aliphatic chain, morpholine ring and NH_2, m, 7H), 4.93 (H-4, d, *J* = 4.0 Hz, 1H), 5.50 (H-3, d, *J* = 4.0 Hz, 1H), 6.53 (ArH, d, *J* = 8.1 Hz, 2H), 6.95 (ArH, d, *J* = 8.6 Hz, 1H), 7.03 (ArH, S, 1H), 7.12 (ArH, d, *J* = 8.1 Hz, 2H), 7.26-7.69 (ArH, m, 5H). ^{13}C-NMR ($CDCl_3$) δ 24.4 (aliphatic chain), 38.5 (aliphatic chain), 53.6 (morpholine ring), 56.2 (aliphatic chain), 62.2 (C-4), 66.8 (morpholine ring), 81.8 (C-3), 108.9, 114.8, 118.5, 122.1, 124.0, 126.3, 126.8, 127.6, 129.3, 129.4, 129.8, 133.9, 146.9, 154.9 (aromatic carbons), 166.0 (CO, *β*-lactam). MS m/z = 431 [M^+]. Anal. Calcd. for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74%. Found: C, 72.45; H, 6.89; N, 9.69 %.

4-(3-Aminophenyl)-1-(3-morpholinopropyl)-3-phenoxyazetidin-2-one ***(3e)***

Off-white solid (yield 68 %). mp 117-119 °C. IR (KBr, cm^{-1}) 1751 (CO, *β*-lactam), 3356, 3456 (NH_2). ^{1}H-NMR ($CDCl_3$) δ 1.62 (aliphatic chain, m, 2H), 2.25 (aliphatic chain and morpholine ring, m, 6H), 2.95 (aliphatic chain, m, 1H), 3.47 (aliphatic chain, m, 1H), 3.63 (morpholine ring and NH_2, m, 6H), 4.79 (H-4, d, *J* = 4.4 Hz, 1H), 5.35 (H-3, d, *J* = 4.4 Hz, 1H), 6.56 (ArH, d, *J* = 7.7 Hz, 1H), 6.60 (ArH, d, *J* = 8.3 Hz, 1H), 6.66 (ArH, s, 1H), 6.72 (ArH, d, *J* = 8.5 Hz, 2H), 6.99 (ArH, t, *J* = 7.7 Hz, 1H), 7.07 (ArH, t, *J* = 8.5 Hz, 1H), 7.11 (ArH, t, *J* = 7.5 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ 24.4 (aliphatic chain), 38.6 (aliphatic chain), 53.6 (morpholine ring), 56.2 (aliphatic chain), 62.3 (C-4), 66.9 (morpholine ring), 81.9 (C-3), 114.7, 115.4, 115.7, 118.9, 121.9, 129.1, 129.2, 134.2, 146.5, 157.1 (aromatic carbons), 166.1 (CO, *β*-lactam). MS m/z = 382 [M^+]. Anal. Calcd. for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02%. Found: C, 69.45; H, 7.25; N, 10.95 %.

4-(3-Aminophenyl)-1-(3-morpholinopropyl)-3-(naphthalene-2-yloxy)azetidin-2-one ***(3f)***

White solid purified by column chromatography (eluent 5:1 EtOAc/EtOH) (yield 59 %). mp 133-135 °C. IR (KBr, cm^{-1}) 1751 (CO, *β*-lactam), 3348, 3440 (NH_2). ^{1}H-NMR ($CDCl_3$) δ 1.67 (aliphatic chain, m, 2H), 2.34 (aliphatic chain and morpholine ring, m, 6H), 3.02 (aliphatic chain, m, 1H), 3.50 (aliphatic chain, morpholine ring and NH_2, m, 7H), 4.90 (H-4, d, *J* = 4.3 Hz, 1H), 5.52 (H-3, d, *J* = 4.3 Hz, 1H), 6.50 (ArH, d, *J* = 7.9 Hz, 1H), 6.65-7.69 (ArH, m, 10H). ^{13}C-NMR ($CDCl_3$) δ 24.3 (aliphatic chain), 38.7 (aliphatic chain), 53.5 (morpholine ring), 56.1 (aliphatic chain), 62.3 (C-4), 66.7 (morpholine ring), 81.9 (C-3), 109.3, 114.7, 115.5, 118.6, 118.9, 124.1, 126.4, 126.9, 127.6, 129.2, 129.3, 129.5, 133.9, 134.2, 146.5, 154.9 (aromatic carbons), 166.0 (CO, *β*-lactam). MS m/z = 431 [M^+].

Anal. Calcd. for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74%. Found: C, 72.55; H, 6.85; N, 9.69 %.

*Synthesis and Characterization of β-Lactams **(3a-f)** Combined with AgNPs*

Ag NPs were prepared according to a reported procedure. In a typical procedure, 100 mL of the aqueous solution of silver nitrate ($AgNO_3$) (10^{-4} M) was reduced by 0.01 g of sodium borohydride ($NaBH_4$) under Argon atmosphere at room temperature to yield a solution containing AgNPs of 38.2 nm in average diameter. In the next step, 150 mg of *β*-lactams **(3a-f)** was dispersed in 100 mL of the nanosilver solution with stirring. After 12 h, when the color of *β*-lactam was changed from white to light or deep brown, the combined *β*-lactams with AgNPs were separated by centrifugation, washed with distilled water, and dried at 70 °C for further use.

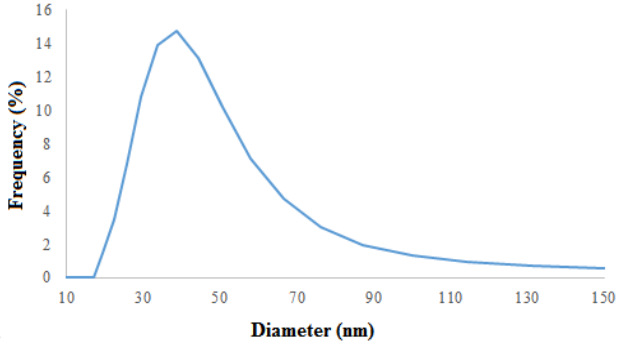


***Figure 3.** DLS of AgNPs.*

Results and discussion

The desired *β*-lactams **2a–f** were prepared via Staudinger reactions of corresponding imines **(1)** with different substituted acetic acids (Scheme 1; Table 1). The *cis* stereochemistry of monocyclic *β*-lactams were deduced from the analysis of their ^{1}H NMR spectra. According to our previous reported paper, the X-ray crystallography of **2f** [29] displayed the *β*-lactam ring was nearly planar, and the morpholine ring was in a chair conformation (Figure 1). Then, to have more electron-rich sites for binding to the electron-deficient AgNPs, monocyclic *β*-lactams **3a–f** bearing NH_2 group from *β*-lactams **2a–f** were synthesized (Table 1). The *cis* stereochemistry of *β*-lactams **3a-f** was deduced from the coupling constant of H-3 and H-4, which was calculated to be J = 4.0–4.5 Hz.

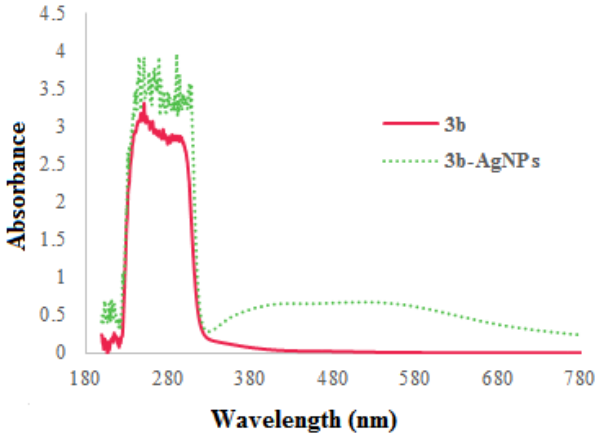


***Figure 4.** The UV-Vis absorption spectra of **3b** and **3b-AgNPs**.*

Colloidal AgNPs were made by adding an excess of the reducing agent sodium borohydride ($NaBH_4$) to $AgNO_3$ solusion. The synthesis of AgNPs was confirmed by the color change of the reaction mixture into pale yellow. UV-visible spectroscopy of the prepared solution (AgNPs) showed a single sharp peak at 400 nm indicating the presence of AgNPs,[30,31] where there are no signals between 300–800 nm range for $AgNO_3$ (Ag^+) indicating no AgNPs before the addition of $NaBH_4$ (Figure 2). Nanoparticles size and distribution obtained by DLS (HORIBA DLS instrument equipped with a laser beam at 550 nm showed the average diameter of AgNPs about 38 nm (Figure 3). Finally, solid amino *β*-lactam each **3a-f** was treated with AgNPs solution for 12 h to obtain its combination with AgNPs; in this process color was changed from white to yellow-brown (Scheme 1).

As an example, the UV-visible spectrum of the solution of **3b** combined with AgNPs (**3b-AgNPs**) showed a broad peak in the range of 400-550 nm, where there is no signal in this range for **3b** (Figure 4). The appearance of the red-shifted peak is attributed to the aggregation of the AgNPs in the presence of compound **3b** or a charge transfer band due to the molecule-metal interaction.[32,33] The SEM images of *β*-lactam **3b (a)** and *β*-lactam **3b** combined with AgNPs **(b)** are shown in Figure 5. The SEM image of **3b** shows layered surfaces, while the image of **3b-AgNPs** shows AgNPs distributed on the surface of **3b** layers.

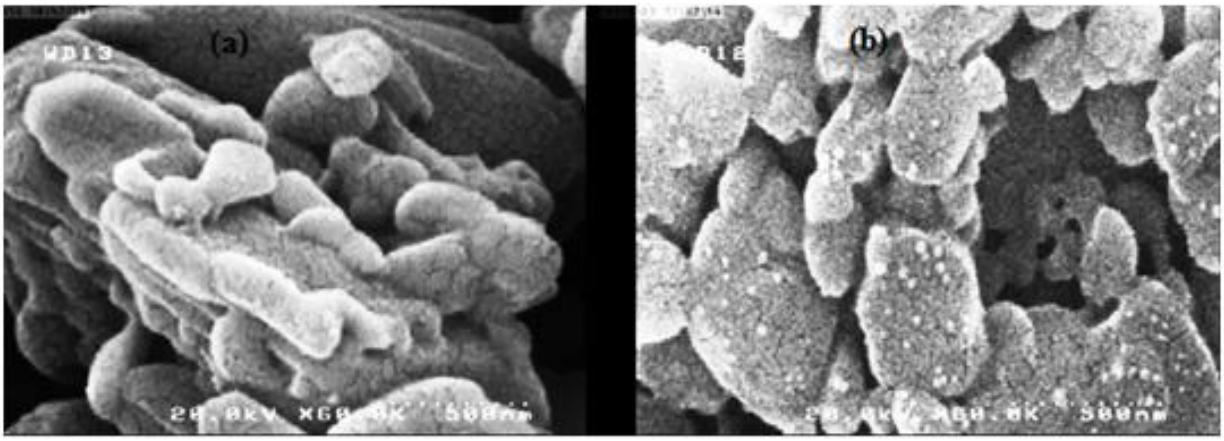


***Figure 5. (a)** SEM Image of **3b** and **(b) 3b-AgNPs**.*

Conclusion

In this study, several monocyclic *β*-lactams bearing biological active moiety morpholine ring have been synthesized. In addition, we use a simple way to the combination those β-lactams bearing NH_2 with AgNPs. SEM image and UV–Vis absorption spectra confirmed the presence of AgNPs on the surface of monocyclic *β*-lactams layes.

Aknowledgments

The authors thank the Shiraz University Research Council for financial support.

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