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ORIGINAL PAPER

Copper-catalyzed thioarylation or thioalkylation of halogenated 2-azetidinones using a thiol precursor

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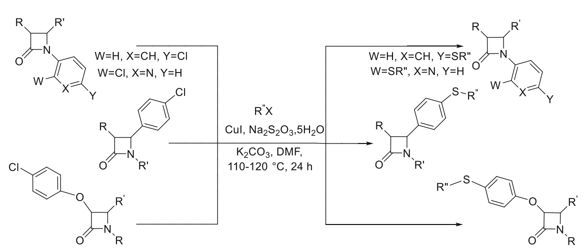
Abstract
The paper describes the synthesis and characterization data of new 2-azetidinones containing sulfide groups. Halogenated 2-azetidinones were synthesized by the reaction of ketenes, generated in situ from various carboxylic acid in the presence of Vilsmeier reagent, with different Schiff bases. These compounds on further reaction with several aryl or alkyl halide using copper(I) iodide and sodium thiosulfate produced novel 2-azetidinones including sulfide substituents in N-1 or C-3 or C-4 position. The compounds have been characterized by elemental analysis and spectral (IR, ^{1}H and ^{13}C NMR) data.

Graphical abstract



Keywords β-Lactam · 2-Azetidinone · Thioarylation · Thioalkylation · Copper-catalyzed

Introduction

β-Lactam antibiotics comprises penicillins, cephalosporins, cephamycins, monobactams, carbacephems, and carbapenems and are so named since they all contain the β-lactam (2-azetidinone) moiety [1]. These miracle antibacterial drugs have served an important and highly successful role in medicine and in pharmaceutical industry [2–4]. Ezetimibe has 2-azetidinone ring in its structure and is used clinically as a cholesterol absorption inhibitor [5]. In addition, 2-azetidinones possess various other biological activities [6–8] and are also used as synthon for the synthesis of several organic compounds [9–11]. Several synthetic methods have been reported for the preparation of the 2-azetidinone ring [12–20].

Sulfur-containing organic molecules are a very important motif; particularly, aryl sulfides and their derivatives are imperative molecules having biological, pharmaceutical, and material interest [21, 22]. Many synthetic methods have been developed for the synthesis of aryl sulfides [21–24]. The development of transition-metal-catalyzed synthesis of aryl sulfides using a thiol precursor is also reported [21, 25–30].

In the past few decades, synthesis of heterocyclic compounds containing nitrogen and sulfur has been of great interest for researchers, due to their potential use in the pharmaceutical and medicinal applications [31].

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Some of β-lactam antibiotics such as penicillins, cephalosporins, and monobactams containing thioether group in their structure [1]. N-Thiolated β-lactams (β-lactam compounds have a sulfur substituent on the nitrogen center) have been synthesized which have been represented a broad family of bioactive molecules and the thiol-substituent was effective at biological activities [32, 33]. Also, series of *N*-sulfonyl monocyclic [34] and 3-thiolated β-lactams [35] have been prepared and evaluated for their in vitro antibacterial and antifungal activities against pathogenic strains.

Hence, according to the above facts, the novel 2-azetidinones having thioether moieties were synthesized using copper-catalyzed thioetherification of 2-azetidinones with thiol precursor.

Results and discussion

We started our studies by synthesis of *cis* 2-azetidinones containing aryl chloride substituents in N-1 or C-3 or C-4 position (Table 1). Previously application of Vilsmeier reagent in the preparation of 2-azetidinones via ketene-imine cycloaddition has been reported [36, 37].

Schiff base **1** on reaction with substituted acetic acid **2** in the presence of Vilsmeier reagent and triethylamine at room temperature afforded cis 2-azetidinones **3a–3f**.

^{1}H NMR spectra of compound **3a–3f** displayed two signals about 5.2 and 5.5 ppm for H-4 and H-3, respectively, with the coupling constant about 4.7 Hz, this clearly indicated the *cis* stereochemistry for 2-azetidinones **3a–3f** (the coupling constant H-3 and H-4 ($J_{3,4} > 4.0$ Hz) for the *cis* stereoisomer and ($J_{3,4} \leq 3.0$ Hz) for the *trans* stereoisomer) [38, 39].

Compound **3a**, treated with iodobenzene in the presence of CuI and S_8 at 110 °C, afforded 2-azetidinone containing thioether **5a**, which was characterized by spectral data and elemental analysis. To improve the yield and find the optimum condition for the synthesis of 2-azetidinone **5a**, next, condition of reaction was investigated. All reactions were monitored by TLC (Table 2).

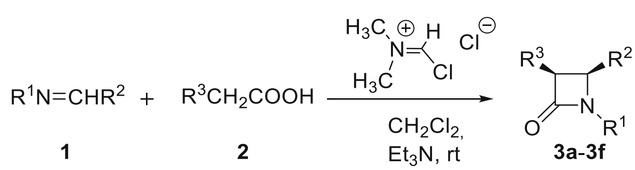
According to Table 2, reaction of 2-azetidinone **3a** and iodobenzene in the presence of CuI as a catalyst, $Na_2S_2O_3{\cdot}5H_2O$ as a sulfur source and K_2CO_3 as a base in dimethylformamide at 110–120 °C is the best condition with the highest yield. The reaction was not performed at room temperature.

With the optimized conditions in hand, the reactions of different 2-azetidinones **3** with various aryl or alkyl halides **4** were examined to explore the scopes of the reaction (Scheme 1). The results were shown in Table 3.

The purity of the compounds was checked by TLC and elemental analysis. Spectral data (IR, ^{1}H NMR, and ^{13}C NMR) of all the compounds were in full agreement with the proposed structures. IR spectra of β-lactams **5a–5p** showed sharp peaks at 1731–1765 cm^{-1} due to β-lactam carbonyl group. Also signal for aldehyde carbonyl group of products **5a**, **5e**, **5h**, **5k**, and **5o** were observed at 1723–1732 cm^{-1}. Their ^{1}H NMR spectra showed well-separated doublet of doublet for H-4 and H-3 protons of cis β-lactams **5a–5p**. The signals appeared at 9.85–10.08 ppm for the carbonyl of CHO group in compounds **5a**, **5e**, **5h**, **5k**, and **5o**. Peaks at 161.8–164.4 ppm were attributed to the 2-azetidinone carbonyl and 190.2–192.4 ppm was referred to the aldehyde carbonyl confirmed by ^{13}C NMR.

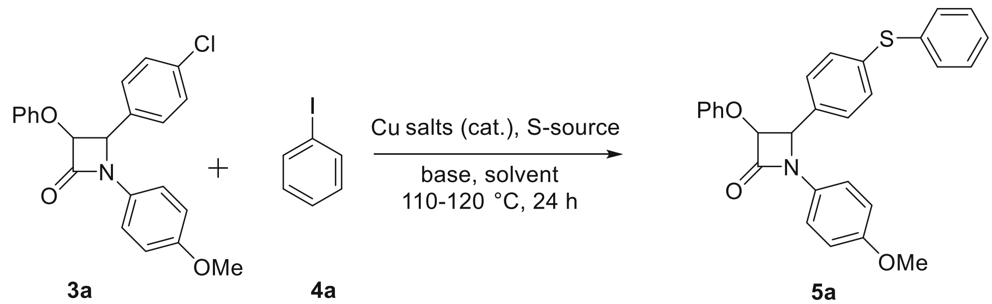
According to a reported mechanism for the thioarylation or thioalkylation using sodium thiosulfate as a thiol precursor [10, 30], it is suggested that the reaction performed via formation of aryl or alkyl thiosulfate and organo-copper intermediates (Scheme 2).

Table 1 Synthesis of 2-azetidinones containing aryl chloride substituents



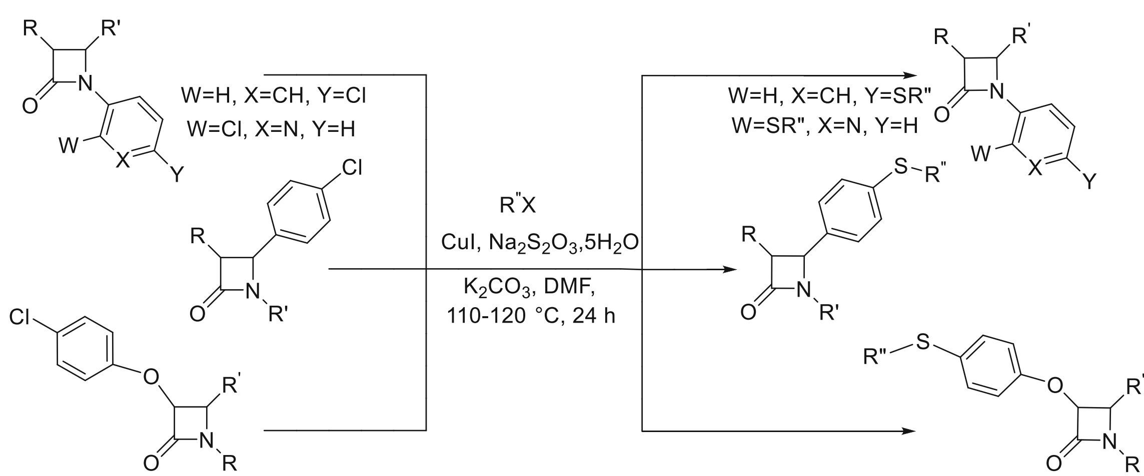
Comp.	R^1	R^2	R^3	Yield/%
3a	4-$MeOC_6H_4$	4-ClC_6H_4	PhO	95
3b	4-$MeOC_6H_4$	4-ClC_6H_4	2-NaphthO	74
3c	4-ClC_6H_4	C_6H_5	PhO	82
3d	4-ClC_6H_4	C_6H_5	2-NaphthO	40
3e	4-$MeOC_6H_4$	C_6H_5	4-ClC_6H_4O	82
3f	2-Cl-3-pyridyl	4-$NO_2C_6H_4$	PhO	88

Table 2 Reaction condition in the synthesis of 2-azetidinone **5a**



Entry	Cu source	S source	Base	Solvent	Yield/%
1	CuI	S_8/KF	K_2CO_3	DMF	70
2	$Cu(OAc)_2$	S_8/KF	K_2CO_3	DMSO	–
3	$Cu(OAc)_2$	S_8/KF	K_2CO_3	PEG400	–
4	$Cu(OAc)_2$	S_8/KF	K_2CO_3	DMF	78
5	CuI	S_8/KF	Cs_2CO_3	DMF	70
6	$Cu(OAc)_2$	S_8/KF	Cs_2CO_3	DMF	60
7	CuI	$Na_2S_2O_3{\cdot}5H_2O$	K_2CO_3	DMF	81
8	$Cu(OAc)_2$	$Na_2S_2O_3{\cdot}5H_2O$	K_2CO_3	DMF	65
9	CuI	$Na_2S_2O_3{\cdot}5H_2O$	Cs_2CO_3	DMF	–
10	$Cu(OAc)_2$	$Na_2S_2O_3{\cdot}5H_2O$	Cs_2CO_3	DMF	36
11	CuI	Thiourea	K_2CO_3	DMF	34
12	$Cu(OAc)_2$	Thiourea	K_2CO_3	DMF	72
13	CuI	Thiourea	Cs_2CO_3	DMF	–
14	$Cu(OAc)_2$	Thiourea	Cs_2CO_3	DMF	–

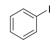
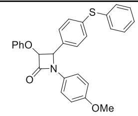
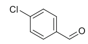
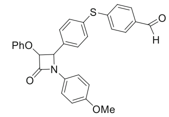
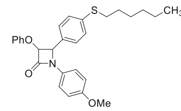
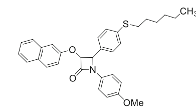
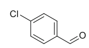
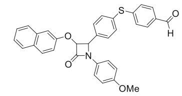
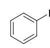
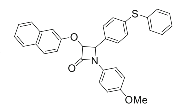
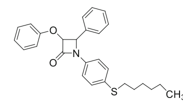
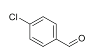
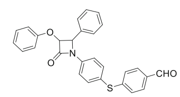
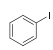
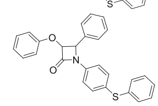
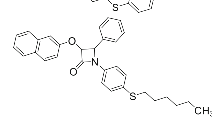
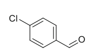
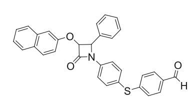
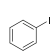
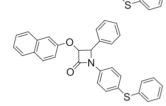
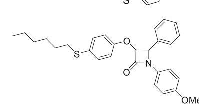
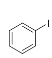
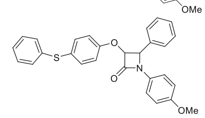
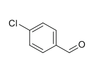
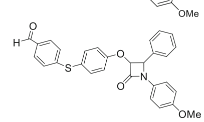
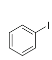
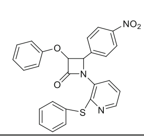
Scheme 1



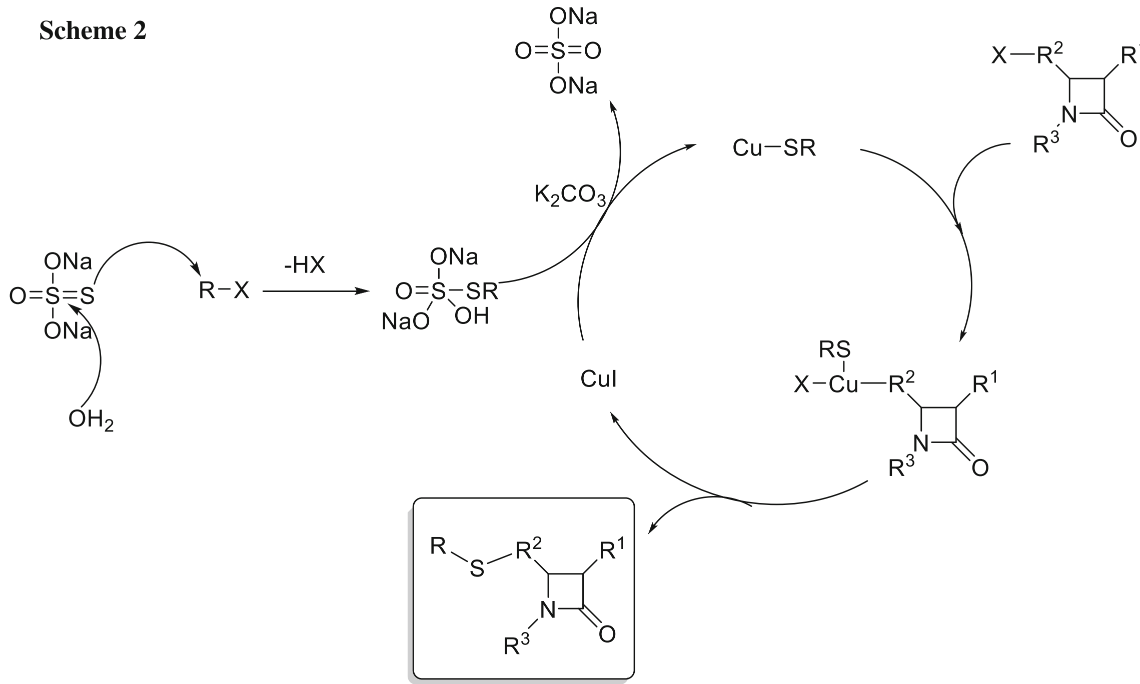
Conclusion

We have developed a protocol for the synthesis of new 2-azetidinones containing sulfide groups in N-1 or C-3 or C-4 position. Copper-catalyzed thioarylation or thioalkylation of halogenated-2-azetidinones using CuI as a catalyst, $Na_2S_2O_3{\cdot}5H_2O$ as a sulfur sources and K_2CO_3 as a base gave desired products in moderate to excellent yields. Purification of products was simple and proceeded without the use of column chromatography.

Table 3 Scope of the thioarylation or thioalkylation of halogenated-2-azetidinones

Entry	2-Azetidinone	R"X		Product	Yield/%
1	**3a**		**5a**		75
2	**3a**		**5b**		88
3	**3a**		**5c**		89
4	**3b**		**5d**		90
5	**3b**		**5e**		53
6	**3b**		**5f**		78
7	**3c**		**5g**		70
8	**3c**		**5h**		40
9	**3c**		**5i**		50
10	**3d**		**5j**		51
11	**3d**		**5k**		45
12	**3d**		**5l**		48
13	**3e**		**5m**		86
14	**3e**		**5n**		70
15	**3e**		**5o**		63
16	**3f**		**5p**		79

Scheme 2



Experimental

All required chemicals were purchased from Merck, Fluka, or Acros chemical companies. The melting points were determined on an Electrothermal 9200 apparatus. IR spectra were measured on a Galaxy series FT-IR 5000 spectrometer. NMR spectra were recorded in DMSO-d_6 using a Bruker spectrophotometer (^{1}H NMR 300 MHz, ^{13}C NMR 75 MHz) with tetramethylsilane as an internal standard and coupling constants were given in cycles per second (Hz). Elemental analyses were run on a Vario EL III elemental analyzer. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka. (Chloromethylene)dimethylammonium chloride (Vilsmeier reagent) **2** was obtained as a white solid by a reported procedure [40]. β-Lactams **3a**–**3f** were prepared according to reported methods and spectral data for **3a**, **3c**, **3e**, and **3f** have been previously reported [41–44].

4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-(naphthalen-2-yloxy)azetidin-2-one (3b, $C_{26}H_{20}ClNO_3$) White solid; m.p.: 181–184 °C; IR (KBr): $\bar{\nu}$ = 1749 (CO, β-lactam) cm^{-1}; ^{1}H NMR (300 MHz): δ = 3.79 (OMe, s, 3H), 5.34 (H-4, d, 1H, J = 5.1 Hz), 5.66 (H-3, d, 1H, J = 5.1 Hz), 6.89–6.95 (ArH, m, 3H), 7.10–7.23 (ArH, d, 2H), 7.30–7.33 (ArH, d, 2H), 7.58–7.61 (ArH, m, 4H), 7.67–7.70 (ArH, m, 4H) ppm; ^{13}C NMR (75 MHz): δ = 56.3 (OMe), 62.1 (C-4), 81.9 (C-3), 110.9, 114.1, 117.9, 120.9, 124.2, 126.0, 126.9, 127.9, 128.4, 129.0, 129.8, 130.9, 131.3, 132.5, 133.8, 135.7, 155.9, 156.6 (aromatic carbons), 162.4 (CO, β-lactam) ppm.

1-(4-Chlorophenyl)-3-(naphthalen-2-yloxy)-4-phenylazetidin-2-one (3d, $C_{25}H_{18}ClNO_2$) Cream color solid; m.p.: 233–237 °C; IR (KBr): $\bar{\nu}$ = 1753 (CO, β-lactam) cm^{-1}; ^{1}H NMR (300 MHz): δ = 5.09 (H-4, d, 1H, J = 4.6 Hz), 5.44 (H-3, d, 1H, J = 4.6 Hz), 6.97–7.24 (ArH, d, 2H), 7.26–7.30 (ArH, m, 11H), 7.32–7.34 (ArH, m, 1H), 7.52–7.73 (ArH, m, 2H) ppm; ^{13}C NMR (75 MHz): δ = 62.1 (C-4), 82.9 (C-3), 111.7, 121.2, 124.2, 126.9, 127.9, 128.3, 128.5, 128.7, 128.9, 129.0, 129.7, 130.6, 131.7, 133.9, 135.9, 138.1, 155.9 (aromatic carbons), 161.9 (CO, β-lactam) ppm.

General procedure for the synthesis of 2-azetidinones 5a–5p A one-necked flask was charged with CuI (0.3 mmol), potassium carbonate (5 mmol), $Na_2S_2O_3\cdot5H_2O$ (1.5 mmol), alkyl/aryl halide (1.25 mmol), 2-azetidinones **3a**–**3f** (1.25 mmol), and 5 cm^3 DMF. The mixture was stirred at 110–120 °C overnight. The reaction mixture was cooled to room temperature. Water (10 cm^3) was added to the reaction mixture, and organics were extracted with EtOAc (3 × 10 cm^3). Evaporation of the solvent followed by purification by crystallization from 95% ethanol provided the corresponding products.

1-(4-Methoxyphenyl)-3-phenoxy-4-[4-(phenylthio)phenyl]azetidin-2-one (5a, $C_{28}H_{23}NO_3S$) White solid; m.p.: 171–174 °C; IR (KBr): $\bar{\nu}$ = 1755 (CO, β-lactam) cm^{-1}; ^{1}H NMR (300 MHz): δ = 3.83 (s, 3H, OMe), 5.20 (d, 1H,

$J = 4.6$ Hz, H-4), 5.62 (d, 1H, $J = 4.6$ Hz, H-3), 6.89–7.03 (m, 5H, ArH), 7.06–7.09 (m, 7H, ArH), 7.10–7.34 (m, 6H, ArH) ppm; ^{13}C NMR (75 MHz): $\delta = 56.3$ (OMe), 61.9 (C-4), 81.7 (C-3), 116.0, 120.4, 122.8, 127.6, 128.5, 128.9, 129.5, 130.8, 132.1, 134.1, 135.0, 135.7, 136.1, 146.1, 156.4, 157.8 (aromatic carbons), 162.1 (CO, β-lactam) ppm.

4-[[4-[1-(4-Methoxyphenyl)-4-oxo-3-phenoxyazetidin-2-yl]-phenyl]thio]benzaldehyde (5b, $C_{29}H_{23}NO_4S$) White solid; m.p.: 173–175 °C; IR (KBr): $\bar{\nu} = 1731$ (CHO), 1754 (CO, β-lactam), 2715, 2804 (CH, aldehyde) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 3.70$ (s, 3H, OMe), 5.22 (d, 1H, $J = 4.9$ Hz, H-4), 5.71 (d, 1H, $J = 4.9$ Hz, H-3), 6.92–7.03 (m, 5H, ArH), 7.11–7.18 (m, 8H, ArH), 7.22–7.33 (d, 2H, ArH), 7.45–7.66 (d, 2H, ArH), 9.90 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz): $\delta = 56.6$ (OMe), 62.0 (C-4), 83.8 (C-3), 114.3, 116.6, 120.5, 122.4, 128.0, 129.8, 130.1, 131.6, 131.6, 134.2, 142.7, 156.0, 157.8 (aromatic carbons), 163.3 (CO, β-lactam), 192.0 (CHO) ppm.

4-[4-(Hexylthio)phenyl]-1-(4-methoxyphenyl)-3-phenoxy-azetidin-2-one (5c, $C_{28}H_{31}NO_3S$) White solid; m.p.: 178–180 °C; IR (KBr): $\bar{\nu} = 1740$ (CO, β-lactam) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 0.99$ (t, 3H, $J = 6.5$ Hz, Me), 1.31–1.40 (m, 6H, 3CH$_2$), 1.76–1.81 (m, 2H, SCH$_2$$\underline{CH_2}$), 2.96 (t, 2H, $J = 5.4$ Hz, SCH$_2$), 3.82 (s, 3H, OMe), 5.28 (d, 1H, $J = 4.4$ Hz, H-4), 5.60 (d, 1H, $J = 4.4$ Hz, H-3), 6.92–7.01 (m, 5H, ArH), 7.13–7.16 (d, 2H, ArH), 7.23–7.33 (m, 6H, ArH) ppm; ^{13}C NMR (75 MHz): $\delta = 14.0$ (Me), 22.9, 28.3, 29.0, 31.6 (CH$_2$), 34.2 (SCH$_2$), 55.9 (OMe), 61.8 (C-4), 84.2 (C-3), 113.9, 116.2, 121.1, 123.0, 129.2, 129.9, 130.9, 138.2, 146.1, 156.0, 158.1 (aromatic carbons), 162.5 (CO, β-lactam) ppm.

4-[4-(Hexylthio)phenyl]-1-(4-methoxyphenyl)-3-(naphthalen-2-yloxy)azetidin-2-one (5d, $C_{32}H_{33}NO_3S$) White solid; m.p.: 184–186 °C; IR (KBr): $\bar{\nu} = 1747$ (CO, β-lactam) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 0.97$ (t, 3H, $J = 6.0$ Hz, Me), 1.29–1.43 (m, 6H, 3CH$_2$), 1.74–1.83 (m, 2H, SCH$_2$-$\underline{CH_2}$), 2.92 (t, 2H, $J = 6.1$ Hz, SCH$_2$), 3.80 (s, 3H, OMe), 5.36 (d, 1H, $J = 4.8$ Hz, H-4), 5.69 (d, 1H, $J = 4.8$ Hz, H-3), 6.86–7.10 (d, 2H, ArH), 7.12–7.30 (d, 2H, ArH), 7.32–7.36 (m, 7H, ArH), 7.54–7.61 (m, 2H, ArH), 7.66–7.80 (d, 2H, ArH) ppm; ^{13}C NMR (75 MHz): $\delta = 13.7$ (Me), 23.1, 27.9, 29.1, 32.0 (CH$_2$), 34.9 (SCH$_2$), 55.8 (OMe), 61.5 (C-4), 83.2 (C-3), 111.7, 114.4, 119.0, 120.9, 123.6, 127.3, 127.5, 127.9, 128.6, 129.1, 129.5, 131.1, 131.4, 132.0, 135.8, 138.6, 156.6, 156.8 (aromatic carbons), 161.8 (CO, β-lactam) ppm.

4-[[4-[1-(4-Methoxyphenyl)-3-(naphthalen-2-yloxy)-4-oxo-azetidin-2-yl]phenyl]thio]benzaldehyde (5e, $C_{33}H_{25}NO_4S$) White solid; m.p.: 131–135 °C; IR (KBr): $\bar{\nu} = 1723$ (CHO), 1744 (CO, β-lactam), 2703, 2792 (CH, aldehyde) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 3.65$ (s, 3H, OMe), 5.16 (d, 1H, $J = 4.6$ Hz, H-4), 5.48 (d, 1H, $J = 4.6$ Hz, H-3), 6.87–7.10 (d, 2H, ArH), 7.10–7.12 (m, 4H, ArH), 7.28–7.33 (m, 5H, ArH), 7.34–7.55 (m, 6H, ArH), 7.60–7.66 (m, 1H, ArH), 10.08 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz): $\delta = 55.6$ (OMe), 60.8 (C-4), 80.9 (C-3), 110.9, 113.9, 118.7, 120.7, 123.9, 126.9, 127.6, 128.2, 128.7, 129.4, 129.9, 130.0, 131.1, 131.6, 133.5, 134.0, 135.1, 135.3, 136.1, 143.0, 152.7, 156.8 (aromatic carbons), 164.0 (CO, β-lactam), 192.4 (CHO) ppm.

1-(4-Methoxyphenyl)-3-(naphthalen-2-yloxy)-4-[4-(phenylthio)-phenyl]azetidin-2-one (5f, $C_{32}H_{25}NO_3S$) Crème-color solid; m.p.: 172–175 °C; IR (KBr): $\bar{\nu} = 1758$ (CO, β-lactam) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 3.72$ (s, 3H, OMe), 5.31 (d, 1H, $J = 4.7$ Hz, H-4), 5.63 (d, 1H, $J = 4.7$ Hz, H-3), 6.90–7.09 (m, 9H, ArH), 7.11–7.33 (m, 8H, ArH), 7.50–7.70 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz): $\delta = 55.7$ (OMe), 61.6 (C-4), 81.8 (C-3), 111.7, 113.7, 118.1, 121.2, 123.5, 126.9, 127.0, 127.7, 127.9, 128.6, 129.3, 129.8, 131.2, 131.5, 133.8, 135.1, 135.3, 135.9, 136.2, 155.7, 156.2 (aromatic carbons), 162.2 (CO, β-lactam) ppm.

1-[4-(Hexylthio)phenyl]-3-phenoxy-4-phenylazetidin-2-one (5g, $C_{27}H_{29}NO_2S$) White solid; m.p.:193–196 °C; IR (KBr): $\bar{\nu} = 1765$ (CO, β-lactam) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 0.99$ (t, 3H, $J = 6.1$ Hz, Me), 1.27–1.40 (m, 6H, 3CH$_2$), 1.66–1.77 (m, 2H, SCH$_2$$\underline{CH_2}$), 2.88 (t, 2H, $J = 8.0$ Hz, SCH$_2$), 5.10 (d, 1H, $J = 5.2$ Hz, H-4), 5.54 (d, 1H, $J = 5.2$ Hz, H-3), 6.84–7.00 (m, 3H, ArH), 7.10–7.13 (d, 2H, ArH), 7.23–7.40 (m, 9H, ArH) ppm; ^{13}C NMR (75 MHz): $\delta = 12.9$ (Me), 22.8, 28.7, 29.1, 32.0 (CH$_2$), 34.4 (SCH$_2$), 64.0 (C-4), 83.8 (C-3), 116.4, 122.8, 124.6, 126.7, 127.9, 128.3, 129.4, 133.9, 134.7, 136.0, 147.2, 159.2 (aromatic carbons), 164.4 (CO, β-lactam) ppm.

4-[[4-(2-Oxo-3-phenoxy-4-phenylazetidin-1-yl)phenyl]thio]-benzaldehyde (5h, $C_{28}H_{21}NO_3S$) Cream solid; m.p.: 245–249 °C; IR (KBr): $\bar{\nu} = 1724$ (CHO), 1757 (CO, β-lactam), 2709, 2811 (CH, aldehyde) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 5.24$ (d, 1H, $J = 5.0$ Hz, H-4), 5.50 (d, 1H, $J = 5.0$ Hz, H-3), 6.94–7.07 (m, 5H, ArH), 7.22–7.38 (m, 11H, ArH), 7.61–7.63 (d, 2H, ArH), 9.89 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz): $\delta = 60.8$ (C-4), 83.6 (C-3), 113.7, 122.5, 122.6, 127.0, 127.9, 128.6, 129.4, 130.1, 131.1, 132.0, 133.3, 133.7, 134.6, 138.8, 143.3, 158.9 (aromatic carbons), 164.1 (CO, β-lactam), 190.2 (CHO) ppm.

3-Phenoxy-4-phenyl-1-[4-(phenylthio)phenyl]azetidin-2-one (5i, $C_{27}H_{21}NO_2S$) White solid; m.p.: 240–244 °C; IR (KBr): $\bar{\nu} = 1746$ (CO, β-lactam) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 5.26$ (d, 1H, $J = 4.9$ Hz, H-4), 5.57 (d, 1H, $J = 4.9$ Hz, H-3), 6.91–7.24 (m, 8H, ArH), 7.25–7.38 (m, 11H, ArH) ppm; ^{13}C NMR (75 MHz): $\delta = 62.3$ (C-4), 82.2 (C-3), 109.3, 117.0, 122.8, 126.7, 127.8, 127.9, 128.6, 129.6, 129.9, 130.9, 131.6, 133.7, 134.5, 135.3, 138.0, 157.7, (aromatic carbons), 161.9 (CO, β-lactam) ppm.

1-[4-(Hexylthio)phenyl]-3-(naphthalen-2-yloxy)-4-phenylazetidin-2-one (5j, $C_{31}H_{31}NO_2S$) Cream solid; m.p.: 240–244 °C; IR (KBr): $\bar{\nu}$ = 1753 (CO, β-lactam) cm^{-1}; ^1H NMR (300 MHz): δ = 0.98 (t, 3H, J = 6.0 Hz, Me), 1.26–1.40 (m, 6H, $3CH_2$), 1.62–1.72 (m, 2H, $SCH_2\underline{CH_2}$), 2.90 (t, 2H, J = 7.9 Hz, SCH_2), 5.26 (d, 1H, J = 4.5 Hz, H-4), 5.53 (d, 1H, J = 4.5 Hz, H-3), 7.04–7.20 (d, 2H, ArH), 7.22–7.35 (m, 10H, ArH), 7.50–7.72 (m, 4H, ArH) ppm; ^{13}C NMR (75 MHz): δ = 15.3 (Me), 21.9, 27.9, 28.8, 31.7 (CH_2), 35.2 (SCH_2), 62.4 (C-4), 81.7 (C-3), 111.7, 115.7, 123.9, 124.4, 126.8, 127.3, 127.5, 128.1, 128.4, 128.9, 131.5, 135.5, 136.1, 154.9, (aromatic carbons), 160.6 (CO, β-lactam) ppm.

4-[[4-[3-(Naphthalen-2-yloxy)-2-oxo-4-phenylazetidin-1-yl]-phenyl]thio]benzaldehyde (5k, $C_{32}H_{23}NO_3S$) Cream solid; m.p.: 300–303 °C; IR (KBr): $\bar{\nu}$ = 1732 (CHO), 1759 (CO, β-lactam), 2706, 2801 (CH, aldehyde) cm^{-1}; ^1H NMR (300 MHz): δ = 5.35 (d, 1H, J = 4.7 Hz, H-4), 5.62 (d, 1H, J = 4.7 Hz, H-3), 6.98–7.21 (d, 2H, ArH), 7.22–7.34 (m, 12H, ArH), 7.36–7.68 (m, 5H, ArH), 9.85 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz): δ = 61.5 (C-4), 84.2 (C-3), 107.5, 110.9, 122.2, 124.2, 126.4, 127.5, 127.6, 128.8, 129.1, 129.9, 130.8, 131.1, 131.5, 133.8, 134.2, 135.3, 138.0, 156.3 (aromatic carbons), 162.2 (CO, β-lactam), 191.3 (CHO) ppm.

3-(Naphthalen-2-yloxy)-4-phenyl-1-[4-(phenylthio)phenyl]-azetidin-2-one (5l, $C_{31}H_{23}NO_2S$) Pale-yellow solid; m.p.: 233–235 °C; IR (KBr): $\bar{\nu}$ = 1752 (CO, β-lactam) cm^{-1}; ^1H NMR (300 MHz): δ = 5.19 (d, 1H, J = 4.5 Hz, H-4), 5.47 (d, 1H, J = 4.5 Hz, H-3), 6.95–7.15 (m, 5H, ArH), 7.16–7.20 (m, 13H, ArH), 7.22–7.33 (m, 1H, ArH), 7.39–51 (m, 1H, ArH), 7.52–7.70 (m, 1H, ArH) ppm; ^{13}C NMR (75 MHz): δ = 60.3 (C-4), 81.4 (C-3), 105.9, 107.7, 111.3, 121.9, 124.1, 126.7, 127.4, 127.6, 127.9, 128.3, 128.9, 129.4, 129.7, 131.6, 132.2, 133.6, 135.7, 138.9, 153.4, 157.1 (aromatic carbons), 164.3 (CO, β-lactam) ppm.

3-[4-(Hexylthio)phenoxy]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (5m, $C_{28}H_{31}NO_3S$) Cream solid; m.p.: 187–189 °C; IR (KBr): $\bar{\nu}$ = 1741 (CO, β-lactam) cm^{-1}; ^1H NMR (300 MHz): δ = 1.00 (t, 3H, J = 6.9 Hz, Me), 1.28–1.40 (m, 6H, $3CH_2$), 1.66–1.77 (m, 2H, $SCH_2\underline{CH_2}$), 2.88 (t, 2H, J = 8.0 Hz, SCH_2), 3.81 (s, 3H, OMe), 5.31 (d, 1H, J = 4.4 Hz, H-4), 5.76 (d, 1H, J = 4.4 Hz, H-3), 6.90–6.95 (m, 4H, ArH), 7.14–7.33 (m, 9H, ArH) ppm; ^{13}C NMR (75 MHz): δ = 14.6 (Me), 22.7, 28.5, 29.3, 31.4 (CH_2), 34.5 (SCH_2), 55.2 (OMe), 63.7 (C-4), 83.9 (C-3), 114.2, 119.1, 120.6, 126.7, 127.9, 128.6, 130.3, 131.4, 133.3, 134.5, 156.5, 157.9 (aromatic carbons), 162.6 (CO, β-lactam) ppm.

1-(4-Methoxyphenyl)-4-phenyl-3-[4-(phenylthio)phenoxy]-azetidin-2-one (5n, $C_{28}H_{23}NO_3S$) Cream solid; m.p.: 164–168 °C; IR (KBr): $\bar{\nu}$ = 1740 (CO, β-lactam) cm^{-1}; ^1H NMR (300 MHz): δ = 3.78 (s, 3H, OMe), 5.30 (d, 1H, J = 4.3 Hz, H-4), 5.74 (d, 1H, J = 4.3 Hz, H-3), 6.66–6.68 (d, 2H, ArH), 7.03–7.09 (m, 3H, ArH), 7.17–7.36 (m, 13H, ArH) ppm; ^{13}C NMR (75 MHz): δ = 55.3 (OMe), 63.5 (C-4), 84.2 (C-3), 114.7, 116.2, 121.3, 126.3, 127.9, 128.0, 128.7, 129.6, 130.9, 131.4, 131.9, 133.3, 134.7, 136.1, 155.2, 158.3 (aromatic carbons), 162.6 (CO, β-lactam) ppm.

4-[[4-[[1-(4-Methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]-oxy]phenyl]thio]benzaldehyde (5o, $C_{29}H_{23}NO_4S$) White solid; m.p.: 185–188 °C; IR (KBr): $\bar{\nu}$ = 1728 (CHO), 1754 (CO, β-lactam), 2717, 2808 (CH, aldehyde) cm^{-1}; ^1H NMR (300 MHz): δ = 3.83 (s, 3H, OMe), 5.15 (d, 1H, J = 4.6 Hz, H-4), 5.51 (d, 1H, J = 4.6 Hz, H-3), 6.81–6.96 (d, 2H, ArH), 7.14–7.25 (d, 2H, ArH), 7.25–7.49 (m, 9H, ArH), 7.65–7.68 (d, 4H, ArH), 9.91 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz): δ = 56.1 (OMe), 61.8 (C-4), 81.1 (C-3), 113.8, 115.9, 120.4, 126.8, 127.9, 128.2, 130.1, 130.8, 131.1, 132.0, 133.8, 134.2, 143.5, 150.9, 156.4, 158.4 (aromatic carbons), 162.3 (CO, β-lactam), 192.2 (CHO) ppm.

4-(4-Nitrophenyl)-3-phenoxy-1-[2-(phenylthio)pyridin-3-yl]-azetidin-2-one (5p, $C_{26}H_{19}N_3O_4S$) White solid; m.p.: 193–195 °C; IR (KBr): $\bar{\nu}$ = 1324, 1528 (NO_2), 1616 (C=N, pyridine ring), 1748 (CO) cm^{-1}; ^1H NMR (300 MHz): δ = 5.21 (d, 1H, J = 5.0 Hz, H-4), 5.47 (d, 1H, J = 5.0 Hz, H-3), 6.88–6.91 (m, 4H, ArH), 7.10 (d, 2H, ArH), 7.22–7.28 (m, 4H, ArH), 7.74–7.79 (m, 4H, ArH), 8.02–8.04 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz): δ = 64.6 (C-4), 83.9 (C-3), 115.9, 118.1, 118.9, 122.0, 124.8, 125.1, 125.6, 127.3, 129.7, 131.0, 135.7, 136.4, 138.5, 142.1, 148.6, 152.4, 157.8 (aromatic carbons), 164.3 (CO, β-lactam) ppm.

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References

1. Cojocel C (2008) Beta-lactam antibiotics. In: De Broe ME, Porter GA, Bennett WM, Deray G (eds) Clinical nephrotoxins. Springer, Boston, p 293
2. Page EI (1992) The chemistry of β-lactams. Blackie Academic and Professional, New York
3. Hwu JR, Ethiraj SK, Hakimelahi GH (2003) Mini Rev Med Chem 3:305

4. Long TE, Turos E (2002) Curr Med Chem Antiinfect Agents 1:251
5. Burnett DA (2004) Curr Med Chem 11:1873
6. Carr M, Greene LM, Knox AJS, Lloyd DG, Zisterer DM, Meegan MJ (2010) Eur J Med Chem 45:5752
7. Mehta PD, Sengar NPS, Pathak AK (2010) Eur J Med Chem 45:5541
8. Basu S, Banik BK (2017) In: Banik BK (ed) Beta-lactams: novel synthetic pathways and applications. Springer, Cham, p 285
9. Alcaide B, Almendros P, Aragoncillo C (2007) Chem Rev 107:4437
10. Ojima I, Delaloge F (1997) Chem Soc Rev 26:377
11. Palomo C, Oiarbide M (2010) In: Banik BK (ed) Topics in heterocyclic chemistry, vol 22. Springer, Berlin, p 211
12. Fu N, Tidwell TT (2008) Tetrahedron 64:10465
13. Zarei M (2013) J Chem Res 37:25
14. Zarei M (2013) Monatsh Chem 144:1021
15. Brandi A, Cicchi S, Cordero FM (2008) Chem Rev 108:3988
16. Zarei M (2012) J Chem Res 36:118
17. Zarei M (2014) Tetrahedron Lett 55:5354
18. Nahmany M, Melman A (2006) J Org Chem 71:5804
19. Zarei M (2017) J Heterocycl Chem 54:1161
20. Keri RS, Hosamani KM, Shingalapur RV, Reddy HRS (2009) Eur J Med Chem 44:5123
21. Prasad DJC, Sekar G (2011) Org Lett 13:1008
22. Feng M, Tang B, Liang SH, Jiang X (2016) Curr Top Med Chem 16:1200
23. Bierbeek AV, Gingras M (1998) Tetrahedron Lett 39:6283
24. Correa A, Carril M, Bolm C (2008) Angew Chem Int Ed 47:2880
25. Rostami A, Rostami A, Ghaderi A (2015) J Org Chem 80:8694
26. Park N, Park K, Jang M, Lee S (2011) J Org Chem 76:4371
27. Firouzabadi H, Iranpoor N, Samadi A (2014) Tetrahedron Lett 55:1212
28. Qiao Z, Wei J, Jiang X (2014) Org Lett 16:1212
29. Qiao Z, Liu H, Xiao X, Fu Y, Wei J, Li Y, Jiang X (2013) Org Lett 15:2594
30. Li Y, Pu J, Jiang X (2014) Org Lett 16:2692
31. Xu P, Yu B, Li FL, Cai XF, Ma CQ (2006) Trends Microbiol 144:398
32. Chen D, Falsetti SC, Frezza M, Milacic V, Kazi A, Cui QC, Long TE, Turos E, Dou PQ (2008) Cancer Lett 268:63
33. O'Driscoll M, Greenhalgh K, Young A, Turos E, Dickey S, Lim DV (2008) Bioorg Med Chem 16:7832
34. Jarrahpour A, Zarei M (2006) Molecules 11:49
35. Zarei M, Mohamadzadeh M (2011) Tetrahedron 67:5832
36. Jarrahpour A, Fadavi A, Zarei M (2011) Bull Chem Soc Jpn 84:320
37. Jarrahpour A, Zarei M (2007) Tetrahedron Lett 48:8712
38. Georg GI (1993) The organic chemistry of β-lactams. Verlag Chemie, New York
39. Zarei M (2014) Monatsh Chem 145:1495
40. Jarrahpour A, Zarei M (2009) Tetrahedron 65:2927
41. Zarei M (2017) J Chem Res 41:246
42. Akkurt M, Karaca S, Jarrahpour A, Zarei M, Buyukgungor O (2005) Acta Crystallogr Sect E 61:776
43. Zarei M, Jarrahpour A, Ebrahimi E, Aye M, Torabi Badrabady SA (2012) Tetrahedron 68:5505
44. Jarrahpour A, Zarei M (2010) Tetrahedron 66:5017