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N-Methylthio β-lactam antibacterials: Effects of the C_3/C_4 ring substituents on anti-MRSA activity

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Abstract—N-Thiolated β-lactams are a new family of antibacterials that inhibit the growth of *Staphylococcus* bacteria. Unlike other β-lactam drugs, these compounds retain their full antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) strains and operate through a different mode of action. The structural features, which give these lactams their biological activity, have not yet been completely defined. Earlier efforts in our laboratory established that the *N*-organothio substituent is essential for antimicrobial activity while other groups at C_3 and C_4 on the lactam ring play a more subtle role. In this present study, we investigate these effects by varying the polar and steric nature of the ring substituents at these two centers. From the data presented herein, it appears that there is a need to balance the lipophilic character of the C_3/C_4 groups to obtain an optimal anti-MRSA activity. The structure–bioactivity profiles more closely relate to the compound's ability to penetrate the bacterial cell membrane to sites of action within the cytoplasm rather than to any specific non-bonding interactions with a biological target. Based on these results, a model for the compounds' mode of action is presented.

1. Introduction

Recently, our laboratories have identified a new family of *N*-methylthio-substituted β-lactams **1** that possess promising antibacterial properties. Curiously, most of this activity is directed toward *Staphylococcus* bacteria, including methicillin-resistant strains of *Staphylococcus aureus* (MRSA).[1] The initial lead compound in these studies, *N*-methylthio β-lactam **2**, was first discovered in our laboratories during routine biological screening.[2] Its potent antibacterial nature was totally unexpected since no other β-lactam compound lacking an ionizable or acidic residue on or near the lactam nitrogen has ever been reported to have antibacterial activity. In fact, the structural features of lactam **2** are entirely unprecedented for a β-lactam antibiotic, with only lipophilic substituents occupying positions on the four-membered ring. Our more recent studies have indicated that lactam **2** and some structurally similar analogues inhibit bacterial growth through a mode of action that is distinctly different from those of penicillin and other bioactive β-lactams.[3] These β-lactams exhibit bacteriostatic activity in certain bacteria including *S. aureus* (Gram-positive) and *Neisseria gonorrhoeae* (Gram-negative), and no detectable cytotoxic effects in normal mammalian fibroblast cells.[4] Being devoid of a hydrophilic ring functionality, these *N*-methylthio β-lactams are completely impervious to β-lactamase cleavage, enabling them to operate at full strength as bacteriostatic agents under conditions that render many of the familiar β-lactam drugs ineffective. The structural features, which impart the molecules their antibacterial properties and resistance to β-lactam hydrolysis, have not yet been assessed in detail. We have, however, established that the *N*-thio substituent is required for an antibacterial activity.[5] The substituents at C_3 and C_4 of the lactam ring also appear to play a secondary role in the biological properties. One of the first issues we addressed in the case of lactam **2** is whether bioactivation by an electrophilic species is required for antibacterial activity. This was considered a possibility because in organic media, electrophilic

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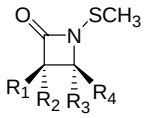
reagents, such as molecular iodine, cause lactam **2** to undergo cyclization to isopenem **3** (Scheme 1).[2] The intermediate in this reaction, bicyclic sulfonium intermediate II, is a powerful alkylating agent that rapidly demethylates in the presence of nucleophiles.



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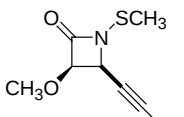

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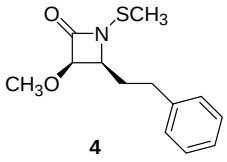
The likelihood that a similar sequence of events could be triggered in vitro was ruled out, however, upon examining phenylethyl lactam **4**, which possessed much of the same activity against MRSA as compound **2**.[6] Thus, π-unsaturation at C_4 is neither a requirement for, nor a detriment to, the antibacterial nature of *N*-methylthio lactams. This was revealed further for propargylic and alkenyl derivatives **5**–**7**, and aryl-substituted lactams **8** and **9**. [5,6] All six of the C_4-varied analogues had antibacterial activity, with **4**, **6**, **8**, and **9** having the strongest growth inhibition of MRSA. This led to the realization that other groups at C_3 or C_4 of the β-lactam ring could alter biological activity, and more information was needed to understand the effects these substituents might have on the compounds' microbiological properties.



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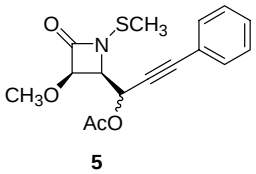

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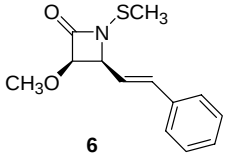

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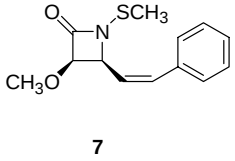

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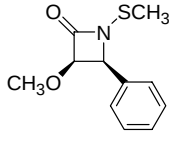

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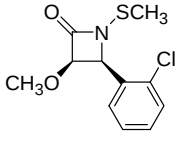

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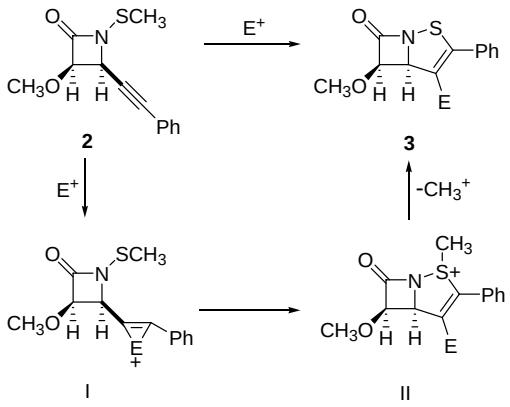
The focus of this present study was thus to understand the primary role of the C_3 and C_4 ring substituents on the anti-MRSA activity of *N*-methylthio β-lactams **1**. Our overall aim was to cover a wide range of structural variations among the C_3/C_4 substituents, differing in their polarities, lipophilicities, steric requirements, hydrogen-bonding capabilities, and stereochemistry. The starting point for us was to consider whether the C_3 methoxy substituent is even needed or whether other types of heteroatomic or non-heteroatomic groups can be tolerated. We also investigated the effect of disubstitution and steric crowding at C_3, before focusing on the



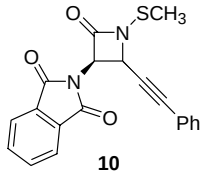
Scheme 1.

analogues of C_4-aryl-substituted lactams **8** and **9** wherein the functionalities, size, and orientation of the aryl substituent are systematically altered. A model which takes into account the experimental results is postulated at the conclusion, to illustrate how we believe these lactams exert their antibacterial effects.

2. Results and discussion

2.1. Synthesis and evaluation of C_3-substituted analogues

Noting that all of the above *N*-methylthio β-lactams **2** and **4**–**9** bear a methoxy group at the C_3 carbon, our first goal was to determine if different types of substituents at this position would affect antibacterial activity. Two derivatives prepared in earlier studies, phthalimidyl compound **10** and benzylthio lactam **11**, were found to be much less active against MRSA than C_3 methoxy lactam **2**.[7] On the other hand, C_3-ethyl derivative **12** is totally devoid of antibacterial activity, contrasting sharply with the strong anti-MRSA properties of structurally similar lactam **6**.



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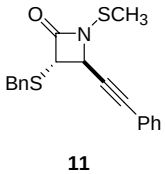

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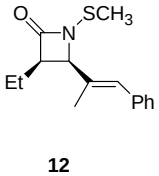
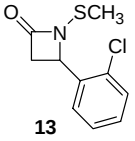


12

Prior to initiating more detailed investigations, we decided to examine C_3-unsubstituted compounds **13**–**15**.[8]



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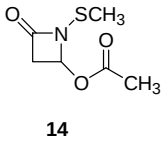

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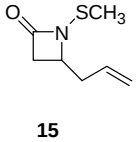

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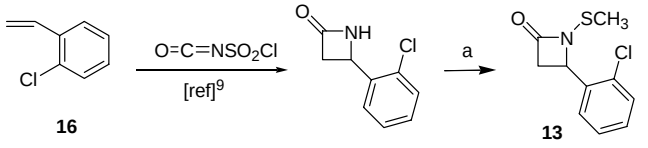
Derivative **13** was obtained by the [2+2]-cycloaddition[9] of 2-chlorostyrene (**16**) with *N*-chlorosulfonylisocyanate, followed by *N*-thiolation with *N*-methylthiophthalimide[10] and triethylamine (Scheme 2).

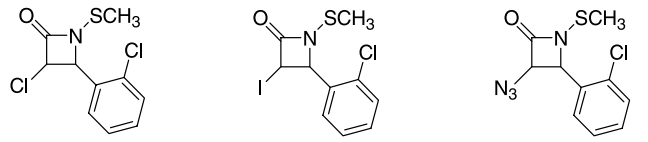


Scheme 2. Reagents and condition: (a) *N*-methylthiophthalimide, Et_3, CH_2Cl_2, rt.

Compounds **14** and **15** were synthesized from commercially available 4-acetoxyazetidinone (**17**) as shown in Scheme 3. *C*-Allylation of **17** using allyltrimethylsilane and BF_3-etherate[11] gave C_4-allyl lactam **18**. N-Thiolation of **17** and **18** gave *N*-methylthio lactams **14** and **15**, respectively.

Of these three C_3-unsubstituted lactams, compounds **13** and **14** had only weak anti-MRSA activity, while allyl derivative **15** was completely inactive. This suggests that a polar C_3 group, in combination with an appropriate C_4 substituent, may be required for bioactivity of these lactams.

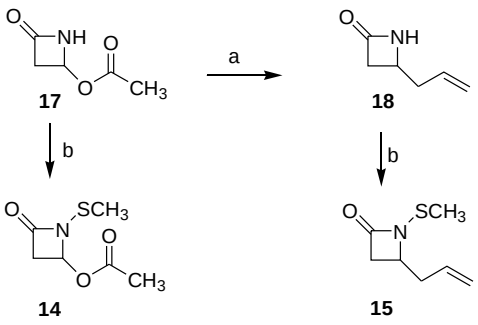
Thus, we then moved on to begin our studies on C_3-substituted lactams, beginning with C_3-halo compounds **19a** and **19b**, and the azido derivative **19c**.



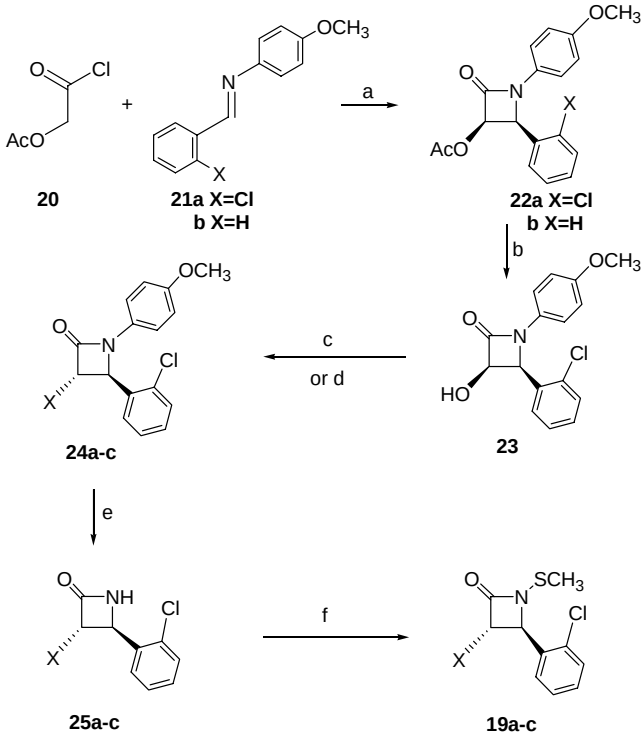
C_3-Halogenated and azido β-lactams can normally be prepared by the Staudinger coupling of an imine with an α-halo or α-azidoacetyl chloride.[12] However, we found it more convenient to access these three lactams directly from C_3-hydroxy β-lactam **23**, which is easily synthesized in two steps from acetoxyacetyl chloride **(20)** and *N*-(4-methoxyphenyl)imine **21** (Scheme 4). C_3-Chloro β-lactam **24a** (X = Cl) was obtained in one step from hydroxyl lactam **23** through the action of Ph_3P and a catalytic amount of sodium bicarbonate in refluxing carbon tetrachloride. To obtain the iodo derivative **24b** (X = I), hydroxy lactam **23** was first converted to its mesylate by the reaction of its sodium salt with methanesulfonyl chloride in anhydrous CH_2Cl_2 and then displaced with NaI in DMF at 80 °C. Similarly, azido lactam **24c** (X = N_3) was obtained by the reaction of mesylate intermediate with sodium azide in DMF. In each case, *trans*-disubstituted lactams **24a–c** were obtained exclusively, as revealed by a characteristically small proton NMR coupling constant (J = 1.5–2.5 Hz) for the β-lactam ring protons.[13] These N-protected lactams were then transformed into the *N*-methylthio lactams **19a–c** by N-dearylation/N-thiolation as described above.

2.2. Microbiological testing of C_3/C_4-substituted lactams

The β-lactams that were prepared in this study were individually tested for antibacterial activity against



Scheme 3. Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, allytrimethylsilane, rt; (b) *N*-methylthiophthalimide, Et_3N, CH_2Cl_2, rt.



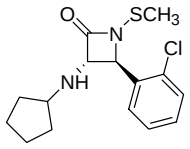
Scheme 4. Reagents and conditions: (a) Et_3N, CH_2Cl_2, rt; (b) NaOH, MeOH, 0 °C; (c) for **24a**: PPh_3, CCl_4, $NaHCO_3$ (catalytic), 70 °C; (d) for **24b**,**c**: NaH, MsCl, CH_2Cl_2, 0 °C to rt; then NaX, DMF, 80 °C; (e) $(NH_4)_2Ce(NO)_6$, MeCN–H_2O, 0 °C; (f) *N*-methylthiophthalimide, Et_3N, CH_2Cl_2, 40 °C (yields vary depending on compound; see Section 4).

methicillin-susceptible and methicillin-resistant *S. aureus* strains by the Kirby–Bauer method of well diffusion on agar plates (Fig. 1). Previously, we have demonstrated that the growth inhibition zone sizes for *N*-methylthio lactams correlate well with their minimum inhibitory concentrations (MICs) obtained from broth dilution experiments, and thus represent a reliable way to gauge bioactivity within a closely related series of analogues.[4a] One MSSA (ATCC 25923), nine MRSA strains (ATCC 43300), and eight clinical isolates from a local hospital) were used for these assays, all of which were β-lactamase producing strains. Table 1 gives the zones of growth inhibition

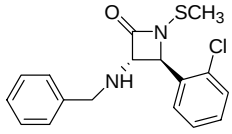
Figure 1. Kirby–Bauer well diffusion assay on an agar plate. The clear regions appearing around the black wells correspond to zones where bacterial growth is inhibited by the diffusing drug. Isolated white spots appearing in this zone, such as that observed for penicillin G (PenG), indicate surviving colonies of resistant bacteria.

for each compound against these microbes. For the purpose of easier visualization, the zone data from these assays are also plotted out graphically, as shown in Figure 2, with the vertical bars indicating the average diameter (from 3 trials) of the growth inhibition zones. The margin of error of these measurements is ±1 mm. It is relevant that for the two reference drugs, penicillin (Pen G) and vancomycin (Van), bioactivity drops precipitously against the MRSA strains, and a closer inspection of the growth inhibition zones for these standards against the MRSA's (see Fig. 1) reveals some speckled regions of bacterial growth indicative of resistant colonies. This is not observed for lactam **9** or any of the other *N*-methylthio β-lactam analogues included in this study. On the other hand, *N*-methylthio lactams **9** and **19a–c** display equal effectiveness against MSSA and MRSA. Of these latter three compounds, chloro derivative **19a** had the strongest activity, with zones of inhibition against the MRSA strains being more than 100% larger than those of penicillin and equal to that of methoxy compound **9**. The iodo and azido-substituted lactams **19b** and **19c** were appreciably weaker in activity than either **9** or **19a**. Thus, for these C_3 varied analogues, the activity follows the trend of $N_3 < I < Cl = OMe$.

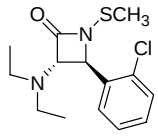
Next, we examined the C_3-amino-substituted analogues **26a–d**, which were synthesized in four steps from hydroxy lactam **23**, as shown in Scheme 5. Moffatt oxidation of **23** with P_2O_5 in DMSO gave ketolactam **27**, which underwent reductive amination using an alkyl- or dialkylamine and $NaBH(OAc)_3$ in a mixture of acetic acid and dichloroethane, to afford amino adducts **28a–d** in good yield.[14] The *trans* stereochemistry was established by ^1H NMR. These PMP-protected compounds were then converted to *N*-methylthio products **26a–d** under the usual N-dearylation/N-methylthiolation conditions. In the case of **26a** and **26b**, the N-thiolation step occurred cleanly on the lactam nitrogen without affecting the 2° amine at C_3.



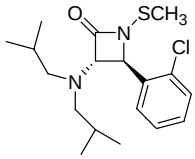
26a



26b



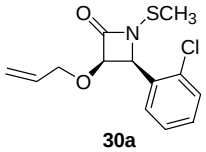
26c



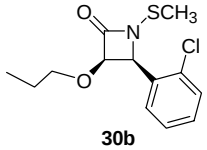
26d

These C_3 amino-substituted analogues turned out to be significantly less potent against MRSA than methoxy compound **9** or the C_3-halo or azido lactams **19a–c**. In fact, only the *N*-benzyl-substituted compound **26b** displayed any activity at all against MRSAs, with average zone sizes of ~11 mm diameter. Thus, amino substituents at C_3 of these *N*-methylthio lactams appear to significantly diminish anti-MRSA activity.

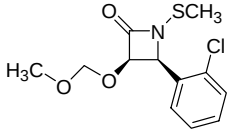
Our next series of analogues consists of a selection of different C_3-oxygenated derivatives of lactams **8** and **9**, including alkoxy and phenoxy derivatives, acyl ester, and sulfonates, to determine if C_3-alkoxy, acyloxy, or sulfonyloxy groups differ in activity. Compounds in this grouping bear a broad range of electronically and sterically distinct functionalities that could affect lipophilicity and bioactivity. Ethers **30a–d**, ester **30e**, and hydroxyl lactam **30f** were examined first.



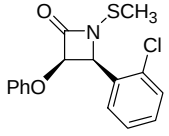
30a



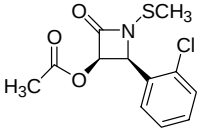
30b



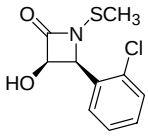
30c



30d



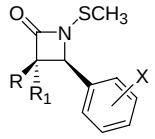
30e



30f

Compounds **30a–c** were synthesized in 3 steps from hydroxy β-lactam **23** by base-induced O-alkylation with the desired alkyl halide, affording *N*-aryl lactams **31a,c**

Table 1. Growth inhibition zones obtained from well diffusion experiments on agar plates



Compound	R	R_1	X	ATCC 43300	USF 652	USF 653	USF 654	USF 655	USF 656	USF 657	USF 658	USF 659
9	OMe	H	2-Cl	28	30	29	28	27	27	25	27	23
19a	N_3	H	2-Cl	23	21	22	22	20	19	21	23	22
19b	I	H	2-Cl	24	20	23	25	23	23	24	25	23
19c	Cl	H	2-Cl	29	30	29	30	30	29	31	30	30
26a	$NHCH(CH_2)_4$	H	2-Cl	0	0	0	0	0	0	0	0	0
26b	$NHCH_2Ph$	H	2-Cl	11	10	12	10	10	10	11	10	10
26c	$N(CH_2CH_3)_2$	H	2-Cl	0	0	0	0	0	0	0	0	0
26d	N^iBu_2	H	2-Cl	0	0	0	0	0	0	0	0	0
30a	OAllyl	H	2-Cl	22	25	24	20	23	23	20	20	24
30b	Opropyl	H	2-Cl	23	24	24	23	22	21	20	20	24
30c	OCH_2OMe	H	2-Cl	15	18	18	19	17	18	18	18	16
30d	OPh	H	2-Cl	16	18	15	15	14	16	13	15	16
30e	OC(O)Me	H	2-Cl	18	23	24	21	23	22	20	21	15
30f	OH	H	2-Cl	18	18	17	17	19	18	16	19	18
33a	OSO_2Me	H	H	15	15	15	18	14	15	15	15	14
33b	OSO_2Ph	H	H	16	17	17	17	15	16	16	15	15
33c	OSO_2Tol	H	H	21	24	20	23	20	20	19	20	21
37a	OAllyl	CH_3	2-Cl	27	28	26	24	26	26	26	24	26
37b	Opropyl	CH_3	2-Cl	26	28	26	24	26	26	25	25	25
37c	OCH_2OMe	CH_3	2-Cl	19	18	17	17	18	17	18	16	18
37d	OAc	CH_3	2-Cl	28	26	28	25	26	28	28	26	23
37e	OAc	Allyl	2-Cl	24	25	26	22	23	25	26	24	21
37f	OAc	Propyl	2-Cl	27	28	27	26	26	28	29	26	24
37g	OAc	Ph	2-Cl	21	20	20	18	20	21	21	20	20
42a	$–O(CH_2)_4–$		H	21	22	19	20	21	20	18	17	21
42d	$–CH_2OCH_2CH_2–$		H	18	17	18	15	16	17	15	16	14
43a	OMe	H	3-Cl	26	25	28	22	23	23	22	19	18
43b	OMe	H	4-Cl	25	26	26	26	25	25	23	24	18
43c	OMe	H	2-F	26	27	28	25	23	26	26	25	21
43d	OMe	H	3-F	20	21	24	18	18	19	21	18	17
43e	OMe	H	4-F	26	25	27	22	21	25	25	23	20
43f	OMe	H	2-I	29	34	29	27	28	29	28	28	23
43g	OMe	H	3-I	24	23	23	21	24	22	25	23	22
43h	OMe	H	4-I	23	27	24	24	24	25	24	20	17
43i	OMe	H	2,4-Cl	22	22	21	21	24	19	20	21	17
43j	OMe	H	2,6-Cl	19	20	21	19	20	21	21	19	16
43k	OMe	H	2,3,5-Cl	23	24	23	23	22	19	22	20	18
43l	OMe	H	$2\text{-}OCH_3$	27	29	32	27	27	28	27	26	23
43m	OMe	H	$2\text{-}CH_3$	23	23	27	23	23	25	23	22	20
43n	OMe	H	$2\text{-}NO_2$	20	18	23	20	22	22	20	21	18
43o	OMe	H	$3\text{-}NO_2$	18	17	22	16	14	18	18	17	11
43p	OMe	H	$4\text{-}CO_2CH_3$	12	13	12	11	14	13	12	12	10
43q	OMe	H	$4\text{-}O_2CCH{=}CH_2$	13	13	12	13	12	13	14	13	10
43r	OMe	H	4-OH	17	14	19	18	18	19	19	18	0
43s	OMe	H	4-Ph	10	10	11	10	10	11	12	9	8
43t	OMe	H	$3,4\text{-}CH_2C_6H_4$	14	13	12	13	13	14	13	11	10
47a	$–O(CH_2)_4–$		$4\text{-}NO_2$	16	17	16	15	17	16	14	12	14

The values indicate the average diameters in mm (of three trials) for the zone of growth inhibition observed after 24 h of incubation at 37 °C. Twenty micrograms of each test compound in DMSO solution was used. All of the microbes listed are β-lactamase producing, methicillin-resistant strains of *Staphylococcus aureus* (MRSA). Those labeled as USF652-659 were obtained from a clinical testing laboratory at Lakeland Regional Medical Center, Lakeland, FL. Error values are within ±1 mm.

(Scheme 6). Phenoxy lactam **31d** (R = Ph) was synthesized directly from phenoxyacetyl chloride and imine **21** under the typical Staudinger coupling conditions, as outlined in Scheme 4.[15]

Likewise, acyl ester **31e** was prepared from hydroxyl lactam **23** by base-promoted acylation. These four *N*-aryl lactams were taken onto their *N*-methylthio lactams **30a**, **c**, **d**, and **e** accordingly. **30b** was obtained from

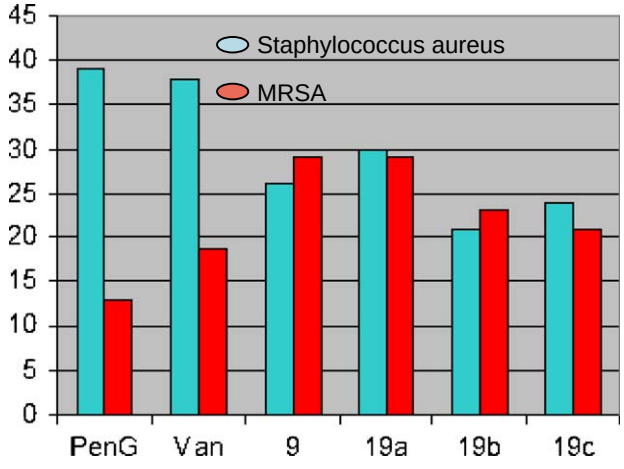


Figure 2. Comparison of antimicrobial activities of lactams **9** and **19a–c** with penicillin G (PenG) and vancomycin (Van) against *Staphylococcus aureus* bacteria. The *y*-axis is the zone of inhibition in millimeters. The vertical bars indicate the average diameter (from 3 trials) of the growth inhibition zones. The blue bars are for methicillin-susceptible *S. aureus* (MSSA), while the red bars are for methicillin-resistant *S. aureus* (MRSA). Thus, the red bars denote the average of 27 trials (9 microbes in triplicate) for each test compound.

32a (R = allyl) by hydrogenation of the allyl group, prior to N-thiolation. Hydroxy lactam **30f** was obtained from **32e** (R = acetyl) by base hydrolysis of the acetate (KOH, MeOH) prior to N-thiolation.

As Figure 3 depicts, lactams **30a–f** all showed enhanced activity against MRSA as compared to penicillin, but an activity lower than that of C_3-methoxy lactam **9**. The relative efficacies of the C_3-oxygenated lactams in this series do vary somewhat, with **9** > **30a** = **30b** = **30e** > **30c** = **30f** > **30d**. Adjusted for their differences in molecular weight, the bioactivities of the lactams **30a–f** show the same trend, suggesting that these slight variations in bioactivity may be due to slightly different lipophilicity and permeability properties of the individual compounds.

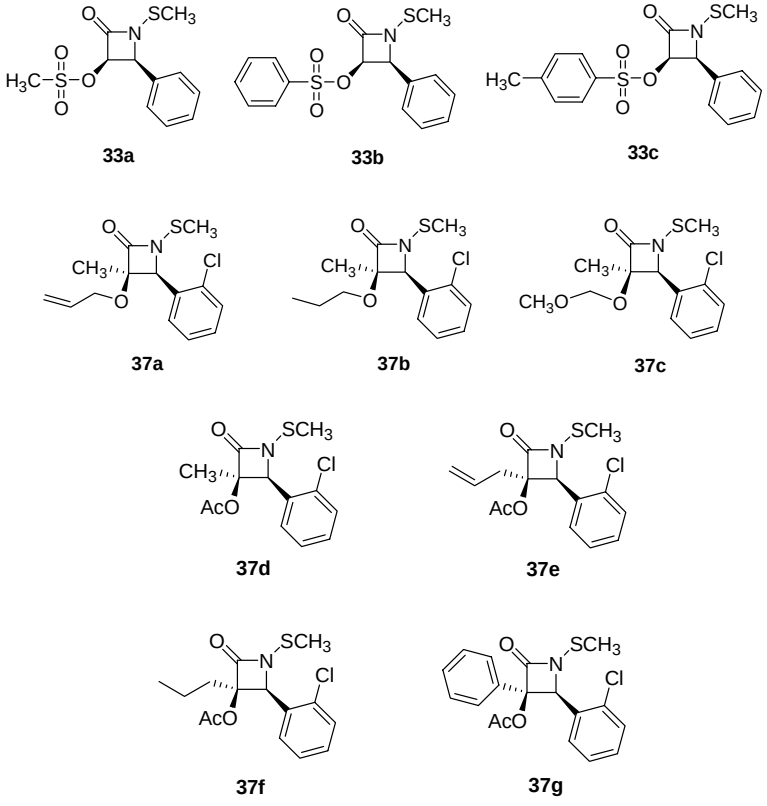
C_3-Sulfonates **33a–c** were also examined in continuation of this series, and their anti-MRSA activities compared to those of C_3-methoxy lactam **8**.

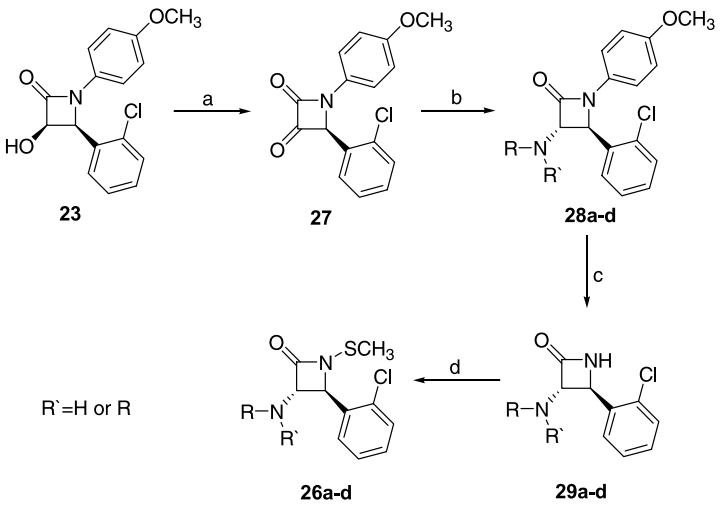
These three new derivatives were prepared via the reaction of the sodium salt of **34** with the appropriate chlorosulfonate, as shown in Scheme 7.

For these three C_3 sulfonates, activity increases with molecular weight: methyl < phenyl < *p*-tolyl (Fig. 4). This trend is also observed in broth MIC values, which range from 64 to 128 μg/mL for the MSSA (ATCC 25923) and MRSA (ATCC 43300) strains. For mesyl compound **33a**, the MICs are all around 128 μg/mL, while for phenylsulfonyl lactam **33b**, the MICs are between 64 and 128 μg/mL, and for the tosyl derivative **33c**, the values decrease to around 64 μg/mL.

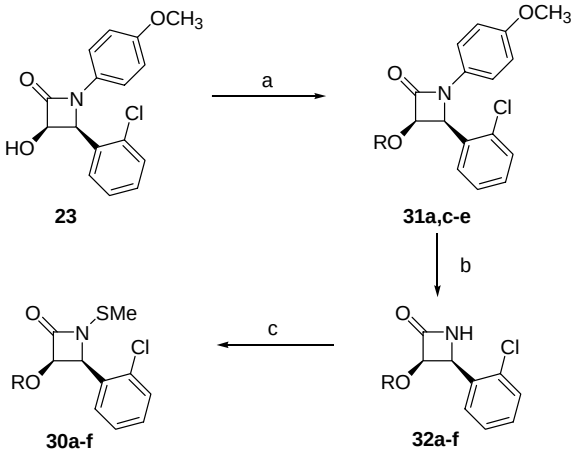
To evaluate the effects of steric crowding at the C_3 center, several differentially configured tertiary ethers **37a–c** and esters **37d–g** of 3,3-disubstituted analogues of **9** were studied next.

These compounds were made from keto β-lactam **27** by introduction of the alkyl or aryl group via Grignard reaction using the method of Buynak (Scheme 8).[16] In each case, nucleophilic attack occurred exclusively





Scheme 5. Reagents and conditions: (a) P_2O_5, DMSO, rt; (b) RR′NH, $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$, rt; (c) $(NH_4)_2Ce(NO)_6$, MeCN–H_2O, 0 °C; (d) *N*-methylthiophthalimide, Et_3N, CH_2Cl_2, 40 °C (yields vary depending on compound; see Section 4).



Scheme 6. Reagents and conditions: (a) for **31a**,**c**,**d**: NaH, R-X, CH_2Cl_2, rt; for **31e**,**f**: AcCl, pyridine, CH_2Cl_2, rt; (b) $(NH_4)_2Ce(NO_3)_6$, MeCN–H_2O, 0 °C, then for **32b**: H_2, Pd/C, rt; (c) *N*-methylthiophthalimide, Et_3N, C_6H_6, 7- °C; for **30f**, KOH, MeOH, 0 °C, then *N*-methylthiophthalimide, Et_3N, C_6H_6, 70 °C (yields vary depending on the compound; see Section 4).

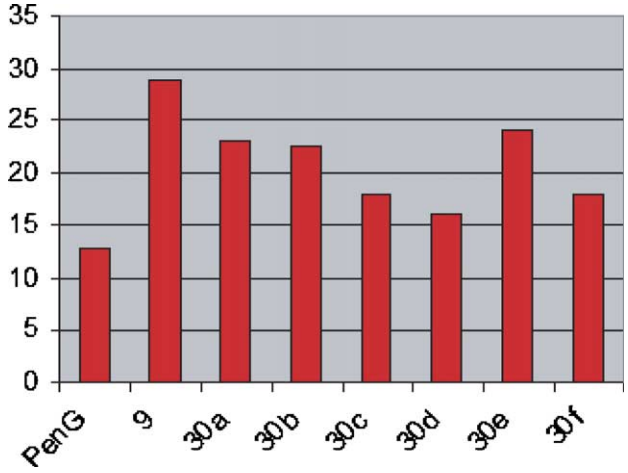
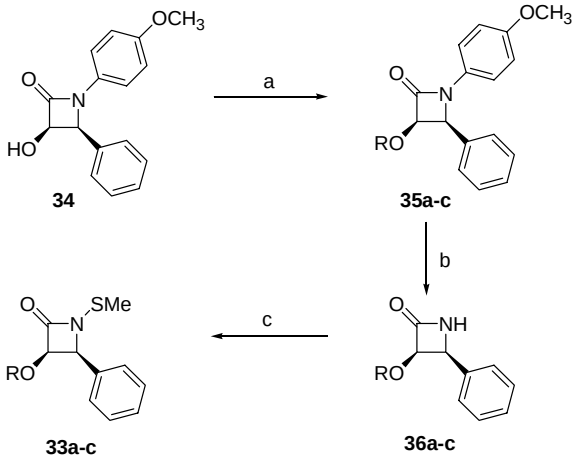


Figure 3. Comparison of antimicrobial activities of lactam **9**, and C_3-alkoxy and C_3-acyloxy lactams **30a**–**f** with penicillin G (PenG). The vertical bars indicate the average diameter in mm of the growth inhibition zones produced against nine different MRSA strains (in triplicate).

from the less hindered α-face to afford β-lactams **38d**–**g**. Relative stereochemistry was established by ROESY NMR. Tertiary alcohol **38d** (R = Me) was then O-alkylated, as described above, and carried on to *N*-methylthio β-lactams **37a**–**c**. Tertiary alcohols **38d**, **e**, and **g** were O-acylated and converted to *N*-methylthio β-lactams **37d**, **e**, and **g**, respectively. β-Lactam **37f** (R = propyl) was obtained from **41e** (R = allyl) by hydrogenation of the allyl group prior to N-thiolation.

The zone data for these seven 3,3-disubstituted compounds indicate that steric crowding on the ring generally diminishes bioactivity, compared to 3-monosubstituted lactam **9** (Fig. 5). In the series of tertiary ethers **37a**–**c**, in which only the ether alkyl moiety is varied, the propyl and allyl ethers **37a**, **b** are more active than the more polar methoxymethyl derivative **37c**. For the second series of compounds, **37d**–**g**, the ether is replaced with an acetoxy ester, while the alkyl side chain is varied. In this case, the saturated alkyl side chain (methyl and propyl) analogues, **37d**,**f**, are at least 33% more active than the lactams **37e**,**g** bearing allyl or phenyl C_3-residues. For these four ester compounds, the MIC values were determined to be between 16 and 64 μg/mL, with the order being **37f** ⩾ **37d** > **37g** ⩾ **37e**. Thus, zone measurements and MIC values indicate the same activity trends.

Finally, to conclude the study of C_3-derivatives, we examined spirocyclic lactams **42a** and **42b**, in which the C_3 ether is contained within a conformationally restricted ring.[17] Compound **42a** had slightly more activity than its isomer **42b**, but was 25% less



Scheme 7. Reagents and conditions: (a) NaH, R-X, CH_2Cl_2, rt; (b) $(NH_4)_2Ce(NO_3)_6$, MeCN–H_2O, 0 °C; (c) *N*-methylthiophthalimide, Et_3N, C_6H_6, 70 °C (yields vary depending on compound; see Section 4).

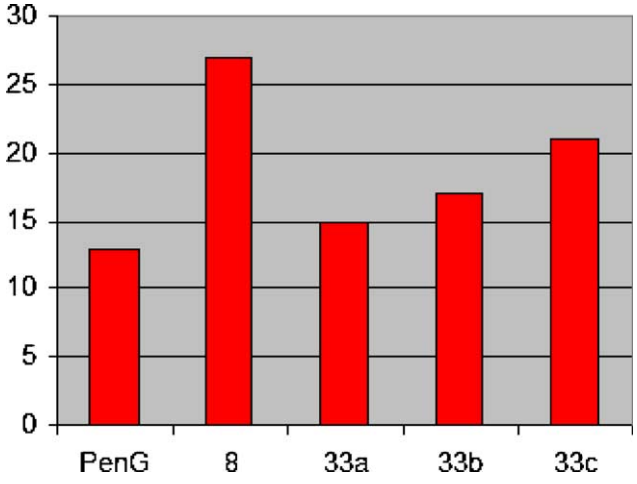
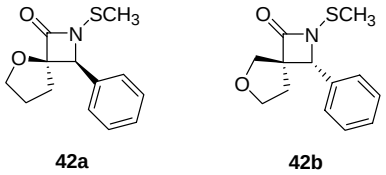


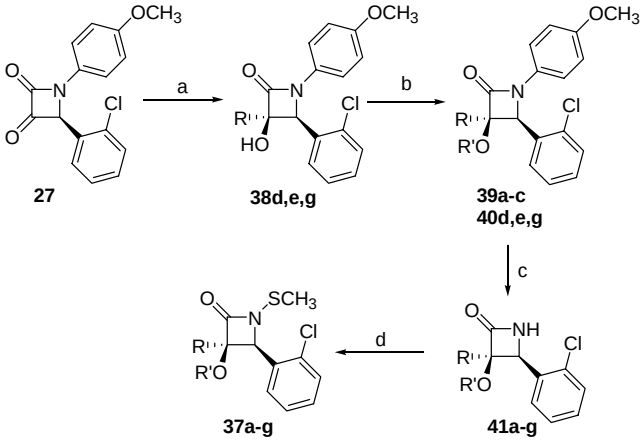
Figure 4. Comparison of antimicrobial activities of lactam **8** and C_3-sulfonate lactams **33a**–**c** with penicillin G (PenG). The vertical bars indicate the average diameter in mm of the growth inhibition zones produced against nine different MRSA strains (in triplicate).

active than the 3° open-ring analogues **37a** and **37b** (Fig. 6).



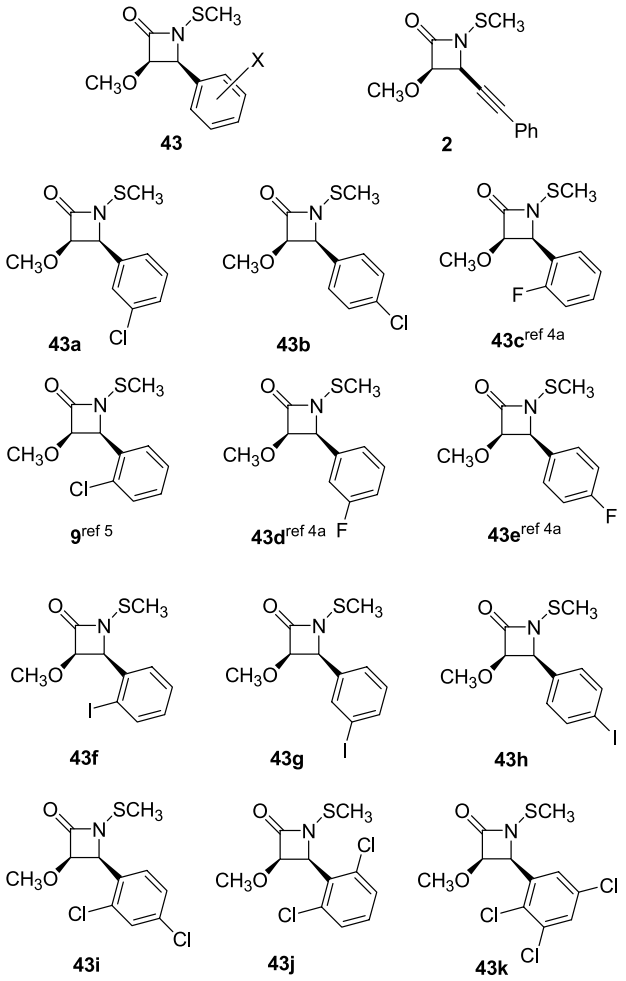
To summarize these findings thus far, it appears that C_3-alkoxy and acyloxy substituents provide for the best anti-MRSA activity.

We then turned our attention to the effects of the C_4 ring substituents on bioactivity. For this study, we chose to look specifically at C_4 aryl-substituted lactams **43**, based upon the observation that the phenyl lactam **8** (X = H in **43**) and chlorophenyl lactam **9** (X = *ortho*-Cl in **43**) had



Scheme 8. Reagents and conditions: (a) RMgBr, THF, NH_4Cl, −78 °C; (b) for **39**–**c**, NaH, R′-X, TBAl, CH_2Cl_2, rt; for **40d**,**e**,**g**, NaH, AcCl, CH_2Cl_2, rt; (c) $(NH_4)_2Ce(NO)_6$. MeCN–H_2O, 0 °C; then fpr **41f**; **41c**, H_2, Pd/C, EtOAc, rt; (d) *N*-methylthiophthalimide, Et_3N, C_6H_6, 70 °C (yields vary depending on compound; see Section 4).

similar antibacterial activity to the C_4-acetylenic lead compound **2**.[4] We have also observed previously that lipophilic substituents at certain locations on the aryl ring of **43** (X = CH_3) seemed to enhance in vitro activities, while more polar groups (X = CN) diminished the activity.[5]



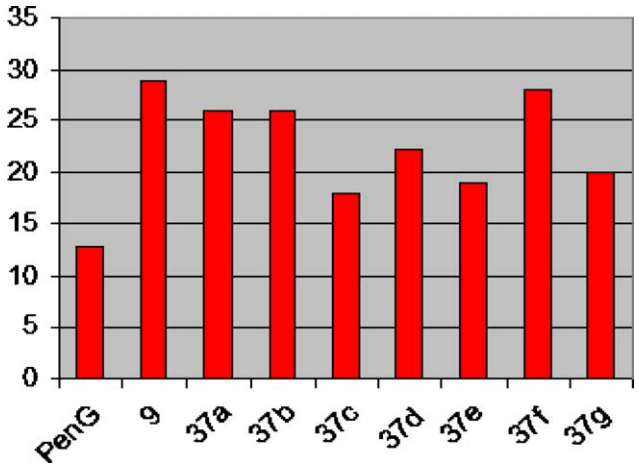


Figure 5. Comparison of antimicrobial activities of lactam **9** and C_3-tertiary ether and ester lactams **37a**–**g** with penicillin G (PenG). The vertical bars indicate the average diameter in mm of the growth inhibition zones produced against nine different MRSA strains (in triplicate).

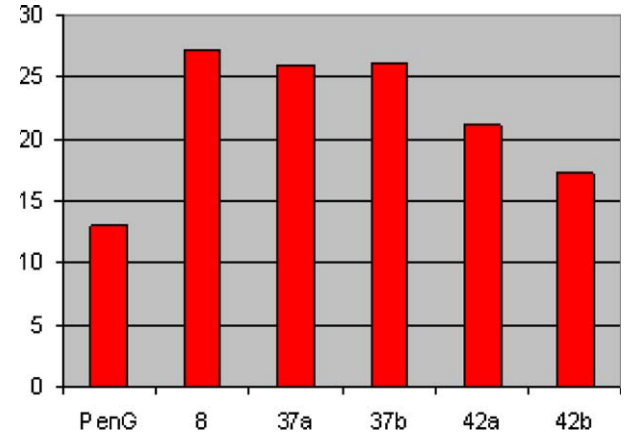
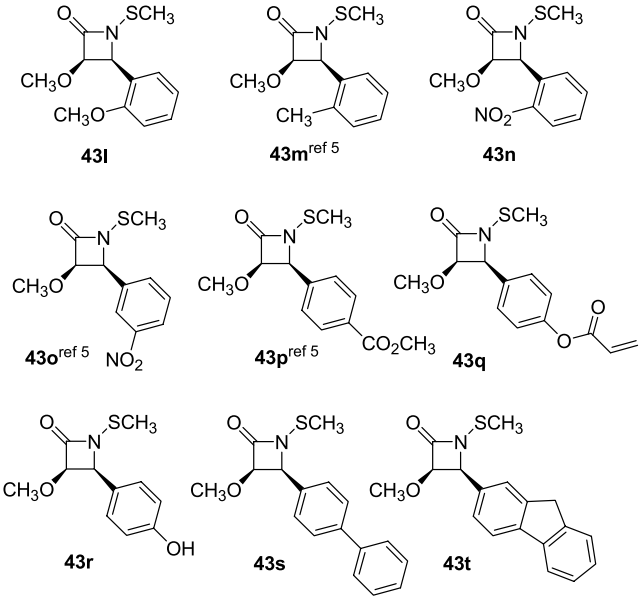


Figure 6. Comparison of antimicrobial activities of lactam **8**, **37a**–**b**, and C_3-spirocyclic lactams **42a**–**b** with penicillin G (PenG). The vertical bars indicate the average diameter in mm of the growth inhibition zones produced against nine different MRSA strains (in triplicate).

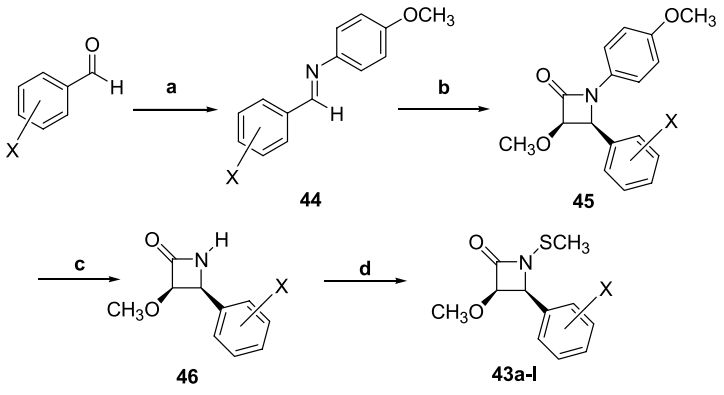
Thus, our next objective was to investigate further the influence of the C_4 aryl ring substituent and the position of the X moiety on the aryl ring on anti-MRSA activity. For this, a focused library of different C_4 aryl-substituted β-lactams, **43a**–**t**, was prepared, as illustrated in Scheme 9. To complement this set, previously reported compounds **43c**–**e**, **m**, **q**, and **r** were also included.



Staudinger coupling of *N*-(4-methoxyphenyl)imines **44** with methoxyacetyl chloride in the presence of three equivalents of triethylamine exclusively afforded the *cis*-disubstituted β-lactams **45**, as corroborated by ^{1}H NMR. These adducts were converted to *N*-methylthio lactams **43**, as previously described.

Figure 7 shows that the location of the variable ring substituent had a discernable effect on activity, with the *ortho* substituents displaying the most potent activities, followed by the groups at the *para* then *meta* positions (**9** > **43e** > **43d**). This agrees with our previous studies of aryl-fluorinated *N*-methylthio β-lactams, which found that those analogues having at least one fluorine *ortho* to the lactam ring displayed the highest potencies, and within the monofluoro series, **43a** > **43c** > **43b**.[4a]

Second, activity among the different halo derivatives is largely independent of which halogen is present on the



Scheme 9. Reagents and conditions: (a) *p*-anisidine, CSA, CH_2Cl_2; (b) CH_3OCH_2COCl, iPr_2EtN, PhMe, 0 ° to rt; (c) $(NH_4)_2Ce(NO_3)_6$, MeCN–H_2O, 0°; (d) *N*-methylthiophthalimide, $^iPr_2EtN$, C_6H_6, 70 °C (yields vary depending on compound; see Section 4).

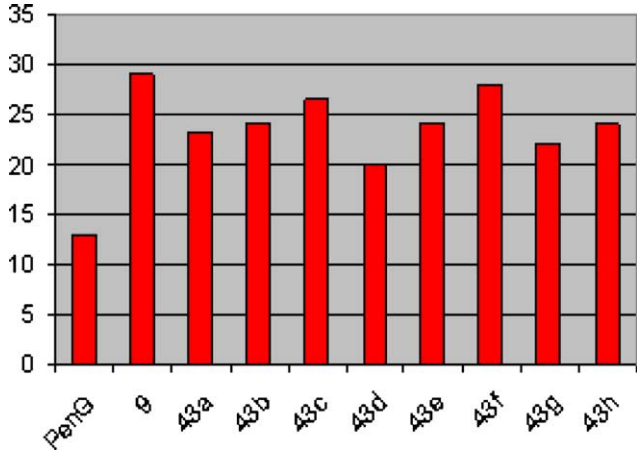


Figure 7. Comparison of antimicrobial activities of lactam **9** and C_4-monohaloaryl lactams **43a–h** with penicillin G (PenG). The vertical bars indicate the average diameter in mm of the growth inhibition zones produced against nine different MRSA strains (in triplicate).

aryl ring (compare the pair of *ortho*-halo compounds **9** to **43a** and **43f**, and *meta*-halo lactams **43b** to **43d** and **43g** in Fig. 7), and the number of halogens on the aryl ring (see lactams **43i–k** in Fig. 8).

Additionally, other monosubstituted aryl analogues **43i–t** were studied to compare the effects of different electron-donating or electron-withdrawing groups on in vitro activity (Fig. 9). What we observe is that replacement of the *ortho*-chloro substituent of lactam **9** for other *ortho* groups, such as methoxy, methyl, or nitro, diminishes activity somewhat, although zone sizes generally remain larger than for the *meta* or *para*-substituted derivatives **43o–t**. Curiously, reversal of the ester functionality at the *para* position (see lactams **43o** and **43r**) does lead to significant reduction of anti-MRSA activity, while conversion of the acryloyl ester **43o** to the corresponding phenol **43p** does not alter activity. Fluorenyl lactam **43s** and biphenyl lactam **43t**, likewise,

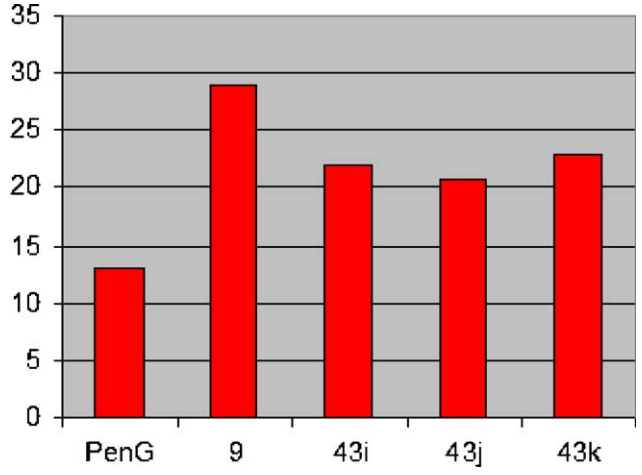


Figure 8. Comparison of antimicrobial activities of lactam **9** and C_4-dihaloaryl and trihaloaryl lactams **43i–k** with penicillin G (PenG). The vertical bars indicate the average diameter in mm of the growth inhibition zones produced against nine different MRSA strains (in triplicate).

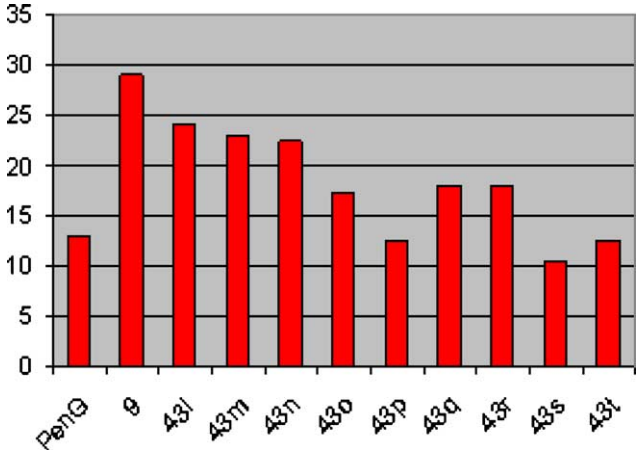
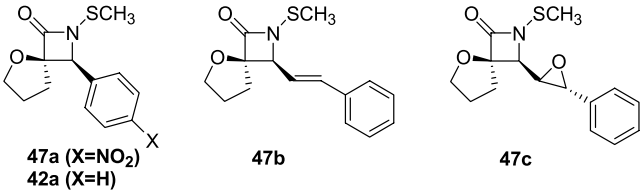


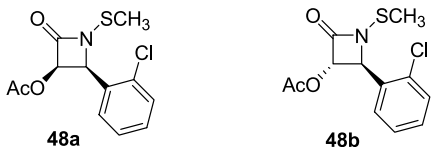
Figure 9. Comparison of antimicrobial activities of lactam **9** and C_4-monosubstituted aryl lactams **43l–t** with penicillin G (PenG). The vertical bars indicate the average diameter in mm of the growth inhibition zones produced against nine different MRSA strains (in triplicate).

show a greatly reduced bioactivity compared to the C_4-phenyl or chlorophenyl analogues **8** and **9**, respectively.

Spiro compounds **47a–c**[17] displayed variable deviations in activity versus C_4 phenyl derivative **42a**. In effect, what these studies indicate is that various types of unsaturated and saturated side chains can occupy the C_4 center without dramatically affecting bioactivity, but *ortho*-substituted aryl ring compounds generally offer better antimicrobial properties (see Fig. 10).



It is also interesting to consider vis-à-vis the *cis* and *trans* stereoisomers of C_3-acetoxy *N*-methylthio β-lactams **48a** and **48b**, which we were able to prepare independently by isolating the *trans* β-lactam adduct from the *cis*/*trans* mixture of *N*-PMP lactams by recrystallization in methanol, and carrying both on to the N-thiolated compounds. These two diastereomers show similar bioactivity with zone sizes in the mid-20 mm range, although the *trans* isomer was found to be about 10% more active than the *cis* lactam.



Likewise, we had the opportunity to examine the effect of absolute stereochemistry on bioactivity through an independent asymmetric synthesis of enantiomeric lactams, (−)-**50a** and (+)-**50a** (Scheme 10). For this, we employed Lipase PS-30 to selectively deacylate the

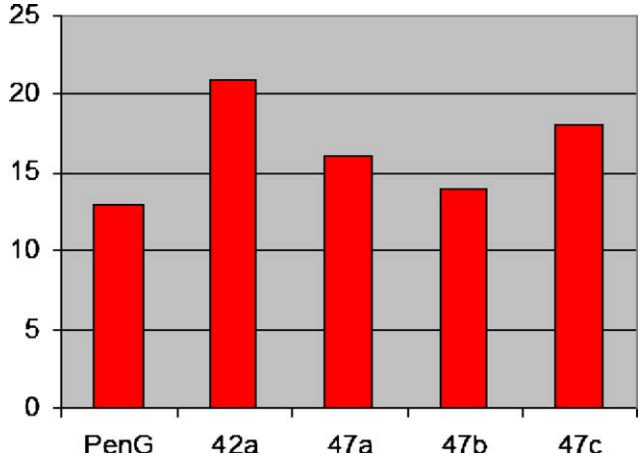


Figure 10. Comparison of antimicrobial activities of C_3-spirocyclic lactams **42a** and **47a–c** with penicillin G (PenG). The vertical bars indicate the average diameter in mm of the growth inhibition zones produced against nine different MRSA strains (in triplicate).

C_3-acetoxy group of the 3S,4R-enantiomer from the mixture of racemic C_3-acetoxy lactams, (±)-**31e**.[18] The resulting enantiomerically pure compounds, (−)-alcohol **49** and recovered (+)-acetate **31e**, were then converted independently to the *N*-methylthio lactams (−)-**50a** and (+)-**50a**, respectively.

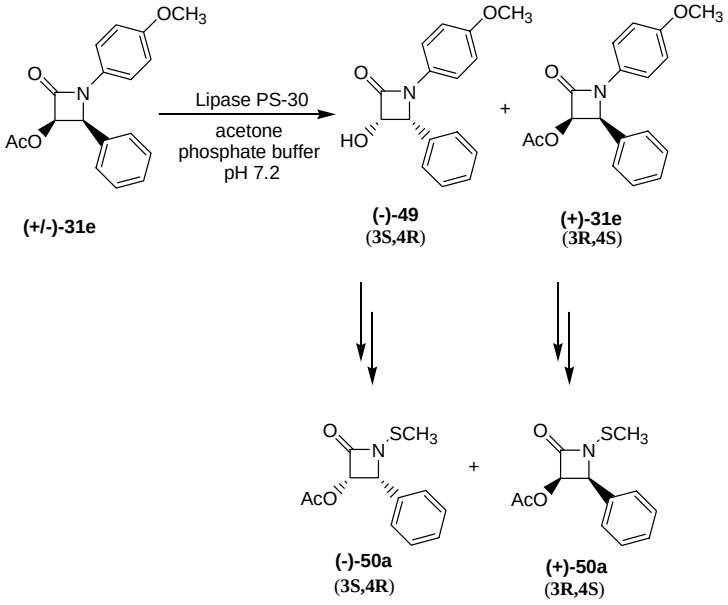
Both antipodes of **50a** displayed equal antimicrobial activity against the MRSA isolates, giving identical zones of growth inhibition on agar plates, as well as equivalent minimum inhibitory concentration (MIC) values in broth dilution experiments. Thus, from these examinations, neither relative nor absolute stereochemistry of the *N*-thiolated lactams seems to be a factor in anti-MRSA activity.

3. Conclusions

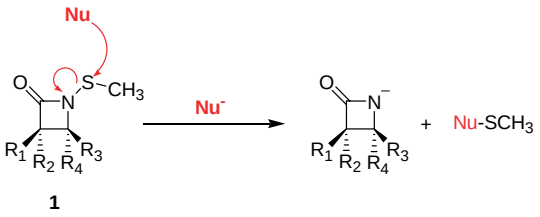
The data in this study reveal some interesting characteristics about the structural requirements of the C_3 and C_4 ring substituents of *N*-methylthio β-lactams. First, lipophilicity within these groups does appear to be required for anti-MRSA activity, although C_3-alkoxy or acyloxy side chains afford the best bioactivity. Differences in the in vitro behavior for all the different analogues may be more closely related to their differences in diffusability through the bacterial membrane, rather than to any specific binding interaction with a biological target. This lends considerable support to the suggestion that the mode of action is as proposed in Scheme 11.

We postulate that the lactams react covalently with their biological target by transfer of the sulfur side chain upon passing through the bacterial cell membrane. Compounds which are too polar to get through the membrane would be expected to have a lower bacteriostatic activity, while those with too much lipophilicity may be sequestered in the membrane or internal organelles, lowering the effective concentration in the cytoplasm. The finding that neither relative nor absolute chirality of the *N*-methylthio lactam affects antimicrobial properties suggests that the lactam may not experience significant non-bonding interactions with its biological target prior to transferring the sulfenyl side chain. This suggests the model shown in Scheme 1 in which the nucleophile attacks the molecule, without precoordination, directly on the sulfur center.

Further work is ongoing to identify the biological target(s) of the lactams in bacterial cells and to determine, in more detail, the effects these compounds have on the primary cellular processes in bacteria.



Scheme 10.



Scheme 11.

4. Experimental

All reagents were purchased from Sigma–Aldrich Chemical Company and used without further purification. Solvents were obtained from Fisher Scientific Company. Thin-layer chromatography (TLC) was carried out using EM Reagent plates with a fluorescence indicator (SiO_2-60, F-254). Products were purified by flash chromatography using J.T. Baker flash chromatography silica gel (40 μm). NMR spectra were recorded in $CDCl_3$ unless otherwise noted. ^{13}C NMR spectra were proton broad-band decoupled.

4.1. Synthesis of 2-chlorophenyl-*N*-(4-methoxyphenyl)-imine (21a)

To a solution of *p*-anisidine (7.27 g, 59.0 mmol) in 50 mL CH_2Cl_2 were added *o*-chlorobenzaldehyde (6.64 g, 47.2 mmol), and a catalytic amount of camphorsulfonic acid. The resultant mixture was stirred until TLC indicated the disappearance of starting materials. The solvent was removed under reduced pressure, and the crude material was purified by recrystallization from ice-cold MeOH to yield 11.41 g (79%) of imine **21a** as a yellow solid. mp 62–63 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 8.95 (1H, s), 8.27–8.23 (1H, m), 7.45–7.36 (3H, m), 7.30 (2H, d, $J = 8.9$ Hz), 6.96 (2H, d, $J = 8.9$ Hz), 3.86 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 156.5, 154.6, 144.5, 135.7, 133.3, 131.7, 129.8, 128.3, 127.0, 122.4, 114.3, 55.4.

4.2. *N*-(4-Methoxyphenyl)phenyl-imine (21b)

White solid in 85% yield. mp 58–60 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 8.42 (1H, s), 7.85–7.82 (2H, m), 7.40 (3H, t, $J = 3.2$ Hz), 7.20–7.15 (2H, m), 6.87 (2H, dd, $J = 2.0$, 7.8 Hz), 3.77 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 156.5, 155.2, 144.2, 132.2.7, 130.3, 128.7, 122.9, 122.4, 114.8, 114.3, 55.9.

4.3. Synthesis of (±)-(3*R*,4*S*)-3-acetoxy-4-(2-chlorophenyl)-*N*-(4-methoxyphenyl)azetidin-2-one (22a)

Imine**21a** (17.3 g, 70.4 mmol) was dissolved in 200 mL of freshly distilled CH_2Cl_2. The solution was cooled to approximately 5 °C in an ice bath. Triethylamine (3 equiv, 21.4 g, 211.4 mmol) was added, followed by acetoxyacetyl chloride (**20**) (1.2 equiv, 11.5 g, 84.4 mmol) dissolved in 20 mL CH_2Cl_2. The reaction mixture was stirred until no further change in TLC was observed for 1 h. The solvent was removed under reduced pressure and the crude material was purified by washing with ice-cold MeOH. The product **22a** was isolated 10.6 g (44%), as a white solid, mp 130–132 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 7.43 (1H, d, $J = 8.9$ Hz), 7.32–7.23 (5H, m), 6.83 (2H, d, $J = 8.9$ Hz), 6.16 (1H, d, $J = 5.0$ Hz), 5.78 (1H, d, $J = 5.0$ Hz), 3.76 (3H, s), 1.76 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.6, 161.3, 156.6, 133.8, 130.1, 129.9, 129.7, 128.6, 126.7, 118.5, 114.4, 75.4, 58.1, 55.3, 19.8.

4.4. (±)-(3*R*,4*S*)-3-Acetoxy-*N*-(4-methoxyphenyl)-4-phenyl-azetidin-2-one (22b)

White solid in 56% yield mp 138–140 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 7.32–7.20 (7H, m), 6.73 (2H, d, $J = 8.9$ Hz), 5.87 (1H, d, $J = 4.8$ Hz), 5.27 (1H, d, $J = 5.0$ Hz), 3.89 (3H, s), 1.60 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.6, 158.1, 142.6, 133.8, 130.1, 129.9, 129.7, 128.6, 126.7, 118.5, 114.9, 114.4, 75.4, 58.1, 55.3, 19.8.

4.5. Synthesis of (±)-(3*R*,4*S*)-4-(2-chlorophenyl)-3-hydroxy-*N*-(4-methoxyphenyl)azetidin-2-one (23)

To a solution of **22** (1.23 g, 3.56 mmol) in 30 mL acetone was added a solution of KOH in 10 mL MeOH at 0 °C. The hydrolysis was complete after the addition of KOH/MeOH, as indicated by TLC. The reaction was quenched by adding an equal volume of water upon which the product precipitated out of solution. The product was filtered and dried to give a white solid, 1.07 g (99%) of **23**, mp 183–184 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 7.48 (1H, d, $J = 7.5$ Hz), 7.33–7.22 (5H, m), 6.84 (2H, d, $J = 8.9$ Hz), 5.63 (1H, d, $J = 5.1$ Hz), 5.33 (1H, d, $J = 5.1$ Hz), 4.88 (1H, br s), 3.78 (3H, s); ^{13}C NMR (63 MHz, DMSO-d_6): δ 166.6, 156.1, 133.1, 132.9, 130.9, 129.7, 129.6, 128.9, 127.3, 118.6, 114.9, 77.2, 60.0, 55.6.

4.6. (±)-(3*R*,4*S*)-3-Hydroxy-4-phenyl-*N*-(4-methoxyphenyl)-azetidin-2-one (34)

White solid in 99% yield, mp 183–184 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 7.49 (1H, d, $J = 7.5$ Hz), 7.32–7.22 (5H, m), 6.83 (2H, d, $J = 8.9$ Hz), 5.62 (1H, d, $J = 5.1$ Hz), 5.33 (1H, d, $J = 5.1$ Hz), 3.77 (3H, s); ^{13}C NMR (63 MHz, DMSO-d_6): δ 166.6, 156.1, 133.1, 132.9, 130.9, 129.7, 129.6, 128.9, 127.3, 118.6, 114.9, 114.2, 77.2, 60.0, 55.6.

4.7. Synthesis of (±)-(3*S*,4*S*)-3-chloro-4-(2-chlorophenyl)-*N*-(4-methoxyphenyl)azetidin-2-one (24a)

To a solution of β-lactam **23** (318 mg, 1 mmol) in 15 mL CCl_4 added triphenylphosphine (524 mg, 2 mmol) and a catalytic amount (1 mg) of $NaHCO_3$ and the mixture was refluxed for 20 h. The solvent was removed under reduced pressure and the crude material was purified by column chromatography using (3:7 EtOAc/hexanes) to give 302 mg (91%) of **24a** as a solid. ^1H NMR (250 MHz, $CDCl_3$): δ 7.40 (1H, d, $J = 7.5$ Hz), 7.10–7.30 (5H, m), 6.80 (2H, d, $J = 7.5$ Hz), 5.40 (1H, d,

J = 1.5 Hz), 4.60 (1H, d, J = 2.0 Hz), 3.70 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 160.0, 156.7, 137.1, 133.8, 133.5, 132.5, 130.3, 128.7, 128.5, 128.4, 127.5, 126.9, 118.8, 114.5, 62.5, 55.4.

4.8. Synthesis of (±)-(3*S*,4*S*)-4-(2-chlorophenyl)-3-iodo-*N*-(4-methoxy-phenyl)azetidin-2-one (24b)

To a solution of β-lactam **23** (795 mg, 2.5 mmol) in 20 mL of dry CH_2Cl_2 was added NaH (60% suspension in mineral oil, 125 mg, 5 mmol) and the mixture was stirred for 15 min. Methanesulfonyl chloride (342 mg, 3 mmol) was then added dropwise to the solution, and the resulting solution was stirred at rt for 30 min. The solution was washed with brine (3× 25 mL), the organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated, and the residue was washed with cold MeOH to give 830 mg as a white solid in 82% yield. To the solution of above compound (405 mg, 1 mmol) dry DMF was added NaI (447 mg, 3 mmol) and the resulting solution was heated to 80 °C for 24 h. After cooling to rt, the solution was concentrated under vacuum. The crude compound was dissolved in EtOAc and washed with water (3× 20 mL), and the organic layer was dried with $MgSO_4$, filtered, and evaporated to give **24b** in 81% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.50 (1H, d, J = 1.0 Hz), 7.25–7.50 (5H, m), 6.83–6.89 (2H, m), 5.57 (1H, d, J = 2.5 Hz), 4.74 (1H, d, J = 2.0 Hz), 3.80 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 162.1, 156.7, 133.5, 130.6, 130.2, 130.0, 129.7, 129.7, 129.6, 126.8, 126.5, 118.8, 118.4, 118.2, 114.0, 62.0, 21.0.

4.9. (±)-(3*S*,4*S*)-3-Azido-*N*-(4-methoxyphenyl)azetidin-2-one (24c)

Brown solid, 81% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.24–7.10 (4H, m), 6.80–6.74 (2H, m), 5.24 (1H, d, J = 1.8 Hz), 4.44 (1H, d, J = 1.8 Hz), 3.70 (3H, s); ^{13}C NMR (63 MHz $CDCl_3$): δ 164.2, 156.2, 142.5, 133.5, 132.2, 128.9, 128.7, 128.2, 127.9, 126.8,121.9, 121.5, 114.2, 113.8, 60.8, 52.2.

4.10. Synthesis of (±)-(4*S*)-4-(2-chlorophenyl)-*N*-(4-methoxyphenyl)-3-oxoazetidin-2-one (27)

Phosphorous pentoxide (0.82 g, 2.88 mmol, 0.7 equiv) was added to 15 mL of dry DMSO. The resultant mixture was stirred for 5 min, followed by the addition of **23** (1.25 g, 4.12 mmol, 1.0 equiv). The reaction was monitored by ^{1}H NMR and showed complete conversion after stirring for 1 h. The reaction mixture was poured into a cold solution of sat. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3× 50 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a yellow solid, 1.16 g (93%) of **27**; mp 127–130 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.49–7.41 (3H, m), 7.35–7.17 (3H, m), 6.89 (2H, d, J = 9.0 Hz), 6.07 (1H, s), 3.78 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 189.5, 159.8, 157.9, 133.3, 130.5, 130.4, 129.5, 129.2, 127.6, 119.5, 114.7, 71.9, 55.4.

4.11. Synthesis of (±)-(3*S*,4*S*)-4-(2-chlorophenyl)-3-cyclopentylamino-*N*-(4-methoxyphenyl)azetidin-2-one (28a)

Cyclopentylamine (35.6 mg, 0.33 mmol) and compound **27** (100 mg, 0.33 mmol) were mixed in $ClCH_2CH_2Cl$ (1.32 mL) and then treated with sodium triacetoxyborohydride (98.6 mg, 0.465 mmol) and AcOH (19.8 mg, 0.33 mmol). The mixture was stirred at rt under a N_2 atmosphere for 1 h until the reactants were consumed completely. The reaction mixture was quenched by adding 1 N NaOH, and the product was extracted with ether. The ether extract was washed with brine and dried with $MgSO_4$. The solvent was evaporated to give **28a** in 88% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30–7.19 (4H, m), 6.90 (2H, d, J = 8.8 Hz), 6.69 (2H, d, J = 8.8 Hz), 4.97 (2H, s), 3.78 (1H, br s), 3.69 (3H, s), 1.71 (4H, m), 1.33 (4H, m); ^{13}C NMR (63 MHz, $CDCl_3$): δ 165.8, 157.9, 140.2, 133.2, 130.5, 130.4, 129.5, 129.2, 127.6, 127.4, 119.5, 114.7, 55.4, 50.0, 48.4, 42.8, 33.3, 33.2, 27.9, 27.8.

An analogous procedure was used to prepare compounds **28b–d**.

4.12. (±)-(3*S*,4*S*)-3-Benzylamino-4-(2-chlorophenyl)-*N*-(4-methoxyphenyl)azetidin-2-one (28b)

95% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.27–7.12 (9H, m), 6.93 (1H, d, J = 8.8 Hz), 6.70 (1H, d, J = 8.8 Hz), 4.96 (2H, s), 4.23 (2H, d, J = 6.0 Hz), 3.69 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 164.0, 161.7, 159.4, 137.8, 134.3, 134.1, 133.9, 133.8, 130.4, 129.4, 129.0, 128.4, 128.2, 127.9, 127.4, 127.1, 119.0, 114.6, 55.7, 53.4, 51.7, 43.5.

4.13. (±)-(3*S*,4*S*)-4-(2-Chlorophenyl)-3-diethylamino-*N*-(4-methoxyphenyl)azetidin-2-one (28c)

90% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.31–7.10 (4H, m), 6.95 (2H, d,J = 8.8 Hz), 6.65 (2H, d, J = 8.8 Hz), 5.00 (2H, s), 3.67 (3H, s), 3.18 (2H, q, J = 7.0 Hz), 3.09 (2H, q, J = 7.1 Hz), 1.14 (3H, t, J = 7.0 Hz), 0.60 (3H, t, J = 7.1 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 164.2, 160.7, 134.2, 132.2, 131.1, 129.7, 129.4, 127.5, 114.5, 55.8, 49.3, 42.3, 37.8, 14.0, 12.2.

4.14. (±)-(3*S*,4*S*)-3-(2-Chlorophenyl)-3-diisobutylamino-*N*-(4-methoxyphenyl)azetidin-2-one (28d)

98% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.31–7.20 (4H, m), 6.96 (2H, d, J = 8.8 Hz), 6.65 (2H, d, J = 8.8 Hz), 4.98 (2H, s), 3.68 (3H, s), 2.90 (4H, t, J = 6.6 Hz), 1.90 (1H, m), 1.45 (1H, m), 0.76 (6H, d, J = 6.6 Hz), 0.35 (6H, d, J = 6.6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 163.1, 156.2, 136.9, 135.2, 134.2, 134.1, 130.2, 129.4 127.5, 122.3, 122.2, 114.2, 114.0, 71.9, 60.0, 56.2, 55.0, 41.6, 28.3, 26.8, 20.6, 20.5, 20.3, 20.2.

4.15. Synthesis of (±)-(3*R*,4*S*)-3-Allyloxy-4-(2-chlorophenyl)-*N*-(4-methoxyphenyl)azetidin-2-one (31a)

To a solution of β-lactam **23** (1.0 g, 3.3 mmol) in 25 mL of dry CH_2Cl_2 was added NaH (60% suspension in

mineral oil, 0.26 g, 6.6 mmol) and the mixture was stirred for 15 min. Allyl bromide (0.79 g, 6.6 mmol) was then added, along with 5 mg TBAI (tetrabutylammonium iodide). The mixture was refluxed for 24 h or until the TLC indicated the disappearance of the starting material. The reaction was quenched with a 5% solution of NH_4Cl and extracted (3× 25 mL) with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography on silica gel (1:9 EtOAc/hexanes) to give 0.92 g (85%) of **31a** as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.43 (1H, d,J = 1.4 Hz), 7.40–7.20 (5H, m), 6.80 (2H, d, J = 9.0 Hz), 5.61 (1H, d, J = 4.7 Hz), 5.09 (2H, d, J = 5.9 Hz), 5.02 (1H, d, J = 4.9 Hz), 3.92 (2H, d, J = 5.5 Hz), 3.73 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 163.8, 156.3, 133.2, 133.0, 131.2, 130.3, 129.4, 129.0, 126.9, 118.6, 118.1, 114.3, 82.5, 71.9, 58.9, 55.4.

4.16. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-3-methoxymethoxy-*N*-(4-methoxyphenyl)azetidin-2-one (31c)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.42 (1H, d, J = 7.8 Hz), 7.26 (5H, m), 6.80 (2H, d, J = 8.8 Hz), 5.64 (1H, d, J = 5.0 Hz), 5.21 (1H, d, J = 5.0 Hz) 4.56 (2H, s), 3.74 (3H, s), 3.19 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 163.9, 156.4, 133.3, 131.5, 130.4, 129.5, 126.9, 118.6, 114.4, 96.6, 80.4, 58.9, 55.7, 55.4.

4.17. Synthesis of 3-acetoxy-*N*-(4-methoxyphenyl)-4-phenylazetidin-2-one (31e)

To a stirred solution of benzaldehyde *N*-(4-methoxyphenyl)imine (5.31 g, 25.2 mmol) and triethylamine (7.64 g, 75.5 mmol) was added a solution of acetoxyacetyl chloride (**20**) (5.15 g, 37.7 mmol) in CH_2Cl_2 dropwise over 10 min. The resultant mixture was stirred at rt until TLC indicated the disappearance of starting material. The solvent was removed under reduced pressure, and the crude material was purified by washing with ice-cold MeOH to give 6.89 g (89%)of **31e** in as white solid, mp 153–155 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.34–7.30 (5H, t), 7.28 (2H, d, J = 8.9 Hz), 6.79 (2H, d, J = 8.9 Hz), 5.92 (1H, d, J = 4.8 Hz), 5.33 (1H, d, J = 4.8 Hz), 3.74 (3H, s), 1.66 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 169.1, 161.2, 156.5, 132.2, 130.2, 128.7, 128.4, 127.8, 118.7, 61.3, 55.3, 19.7.

4.18. Synthesis of (±)-(3*R*,4*S*)-*N*-(4-methoxyphenyl)-3-methylsulfonyl-4-phenylazetidin-2-one (35a)

Compound **34** (269 mg, 1.00 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and 60 mg (1.50 mmol) of NaH (60% in mineral oil, unwashed) was added. After stirring for 30 min at room temperature to the resultant solution methanesulfonyl chloride (115 mg, 1.00 mmol) was then added dropwise. The resultant solution was then stirred at rt for 30 min. The solution was washed with brine (3× 15 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated, and the residue was washed with cold MeOH to give 267 mg (77%) of **35a** as a white solid in; mp 158–160 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.48 (2H, d, J = 7.8 Hz), 7.39–7.26 (7H, m), 6.85 (2H, d, J = 8.7 Hz), 5.94 (1H, d, J = 5.1 Hz), 5.82 (1H, d, J = 5.1 Hz), 3.75 (3H, s), 3.02 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 163.2, 157.3, 132.5, 131.8, 130.2, 129.8, 129.3, 129.1, 128.5, 128.1, 119.4, 114.9, 102.1, 79.8, 61.9, 55.9, 39.2.

An analogous procedure was used to prepare sulfonates **35b** and **35c**.

4.19. (±)-(3*R*,4*S*)-3-Benzenesulfonyl-*N*-(4-methoxyphenyl)-4-phenylazetidin-2-one (35b)

White solid, mp 162–165 °C, 93% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.05 (2H, d, J = 4.0 Hz), 7.75–7.60 (5H, m), 7.50–7.18 (5H, m), 6.79 (2H, d, J = 8.6 Hz), 5.90 (1H, d, J = 5.0 Hz), 5.77 (1H, d, J = 5.0 Hz), 3.74 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 160.7, 157.6, 136.2, 134.5, 133.2, 132.1, 129.6, 129.2, 128.5, 128.2, 127.8 (2C), 127.1 (2C), 119.3 (2C), 114.8 (2C), 79.6, 62.1, 55.8.

4.20. (±)-(3*R*,4*S*)-*N*-(4-Methoxyphenyl)-4-phenyl-3-(4-toluenesulfonyl)azetidin-2-one (35c)

White solid, mp 148–151 °C, 75% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.46 (2H, d, J = 7.9 Hz), 7.36–7.28 (8H, m), 6.77 (2H, d, J = 8.5 Hz), 5.78 (1H, d, J = 4.9 Hz), 5.28 (1H, d, J = 4.9 Hz), 3.73 (3H, s), 2.43 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 161.2, 157.6, 147.2, 138.8, 133.4, 131.9, 130.2 (2C), 129.3, 128.5, 128.2, 127.8 (2C), 127.4 (2C), 119.1 (2C), 114.9 (2C), 79.6, 58.1, 55.8, 22.1.

4.21. Synthesis of (±)-(3*R*,4*S*)-4-(2-chlorophenyl)-3-hydroxy-*N*-(4-methoxyphenyl)-3-methylazetidin-2-one (38d)

To a solution of **27** (0.496 g, 1.65 mmol) in 9 mL of anhydrous THF was added methylmagnesium bromide (0.549 mL, 1.05 mmol, 1.0 equiv) at −40 °C. The resultant solution was stirred for 1 h. The reaction mixture was quenched by adding an equal volume of 5% ammonium chloride at −40 °C. The mixture was warmed to room temperature and extracted with EtOAc (3× 50 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure to yield a yellow solid, 0.383 g (73%) of **38d**. No further purification was necessary. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.47 (1H, d, J = 7.2 Hz), 7.29–7.19 (5H, m), 6.83 (2H, d, J = 8.9 Hz), 5.40 (1H, s), 3.76 (3H, s), 1.83 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.2, 156.4, 133.5, 132.0, 130.4, 129.7, 129.3, 128.1, 126.9, 118.7, 114.4, 83.9, 66.1, 55.4, 21.9.

An analogous procedure was used to prepare compounds **38e**,**g**.

4.22. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-3-hydroxy-*N*-(4-methoxyphenyl)-3-(2-propenyl)azetidin-2-one (38e)

Orange oil, 84% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.47 (1H, d, J = 7.3 Hz), 7.33–7.23 (5H, m), 6.83 (2H, d, J = 8.9 Hz), 5.99–5.93 (1H, m), 5.51 (1H, s), 5.39–5.24 (2H, m), 3.77 (3H, s), 2.90 (2H, d, J = 7.4 Hz);

^{13}C NMR (63 MHz, $CDCl_3$): δ 166.9, 156.4, 133.4, 131.8, 130.9, 130.4, 129.8, 129.4, 128.4, 127.0, 120.8, 118.7, 114.4, 85.6, 63.2, 55.4, 40.1.

4.23. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-3-hydroxy-*N*-(4-methoxyphenyl)-3-phenylazetidin-2-one (38g)

Yellow solid, 79% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.67 (2H, dd, J = 7.6, 2.0 Hz), 7.50–7.29 (10H, m), 6.85 (2H, d, J = 9.2 Hz), 5.68 (1H, s), 3.78 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 166.6, 156.6, 138.2, 133.8, 131.4, 129.9, 129.8, 128.6, 126.9, 125.5, 118.9, 114.4, 87.3, 67.2, 55.4.

4.24. Synthesis of (±)-(3*R*,4*S*)-3-allyloxy-4-(2-chlorophenyl)-*N*-(4-methoxyphenyl)-3-methylazetidin-2-one (39a)

To a solution of β-lactam **38d** (0.10 g, 0.32 mmol) in 5 mL of dry CH_2Cl_2 was added NaH (60% suspension in mineral oil, 0.018 g, 0.48 mmol) and the mixture was stirred for 15 min. Allyl bromide (0.076 g, 0.62 mmol) was then added, along with 5 mg TBAI (tetrabutylammonium iodide). The mixture was refluxed for 24 h or until the TLC indicated the disappearance of the starting material. The reaction was quenched with a 5% solution of NH_4Cl and extracted with CH_2Cl_2 (3× 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography on silica gel (1:9 EtOAc/hexanes) to give 0.07 g (87%) of **39a** as a yellow semisolid. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.42 (1 H, d, J = 7.7 Hz), 7.29–7.13 (5H, m), 6.80 (2H, d, J = 8.8 Hz), 5.46–5.35 (1H, m), 5.32 (1H, s), 4.86–4.79 (2H, m), 3.90–3.85 (2H, m), 3.73 (3H, s), 1.81 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 166.0, 156.3, 133.6, 133.3, 132.1, 130.6, 129.4, 129.1, 128.7, 126.6, 118.6, 116.0, 114.3, 88.5, 66.9, 65.4, 55.3, 19.4.

4.25. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-3-methoxymethoxy-*N*-(4-methoxyphenyl)-3-methylazetidin-2-one (39c)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.43 (1H, d, J = 7.5 Hz), 7.30–7.17 (5H, m), 6.85–6.79 (2H, m), 5.30 (1H, s), 4.59 (2H, s), 3.75 (3H, s), 3.08 (3H, s), 1.84 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 167.2, 156.3, 133.1, 131.3, 130.5, 129.4, 126.7, 118.4, 114.2, 96.6, 81.4, 58.7, 55.6, 55.4, 19.2.

4.26. Synthesis of (±)-(3*R*,4*S*)-3-acetoxy-4-(2-chlorophenyl)-*N*-(4-methoxyphenyl)-3-methylazetidin-2-one (40d)

To a solution of **38d** (0.287 g, 0.903 mmol, 2.0 equiv) in 5 mL of CH_2Cl_2 was added NaH (0.072 g, 3.01 mmol). The resultant suspension was stirred until the bubbling stopped, and then acetyl chloride (0.077 mL, 1.08 mmol, 1.2 equiv) was added via syringe. The reaction was followed by TLC and showed that the reaction was complete immediately after adding the acetyl chloride. The reaction was quenched by adding a 1% solution of $NaHCO_3$ (5 mL) and extracted with EtOAc (3× 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield a yellow oil, 0.275 g (85%) of **40d**. No further purification was necessary. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.42 (1H, d, J = 8.3 Hz), 7.29–7.12 (5H, m), 6.82 (2H, d, J = 8.9 Hz), 5.47 (1H, s), 3.75 (3H, s), 1.94 (3H, s), 1.60 (H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.3, 164.4, 156.4, 134.0, 130.8, 130.4, 129.4, 129.3, 129.2, 126.4, 118.5, 114.3, 86.5, 64.8, 55.3, 20.2, 19.8.

An analogous procedure was used to prepare compounds **40e**,**g**.

4.27. (±)-(3*R*,4*S*)-3-Acetoxy-4-(2-chlorophenyl)-*N*-(4-methoxyphenyl)-3-(2-propenyl)azetidin-2-one (40e)

Orange oil, 99% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.42 (1H, d, J = 7.6 Hz), 7.23 (4H, d, J = 5.0 Hz), 7.17 (1H, d, J = 7.5 Hz), 6.81 (2H, d, J = 8.9 Hz), 5.93 (1H, m), 5.56 (1H, s), 5.29 (2H, m), 3.74 (3H, s), 3.09 (2H, d, J = 7.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.3, 163.5, 156.5, 134.0, 130.8, 130.3, 129.9, 129.5, 126.4, 121.1, 118.6, 114.4, 88.4, 61.8, 55.4, 37.5, 20.2.

4.28. (±)-(3*R*,4*S*)-3-Acetoxy-4-(2-chlorophenyl)-*N*-(4-methoxyphenyl)-3-phenylazetidin-2-one (40g)

Yellow oil, 85% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.81 (2H, d, J = 8.9 Hz), 7.46–7.29 (9H, m), 6.83 (1H, d, J = 8.9 Hz), 6.15 (1H, s), 3.76 (3H, s), 1.68 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 167.8, 162.6, 156.6, 134.7, 130.8, 129.8, 129.7, 129.2, 128.9, 128.5, 126.9, 126.4, 118.8, 114.4, 89.7, 63.5, 55.4, 20.3.

4.29. Synthesis of (±)-(3*S*,4*S*)-3-ahloro-4-(2-chlorophenyl)-azetidin-2-one (25a)

To a solution of lactam **24a** (0.335 g, 1.00 mmol) in CH_3CN (2.2 mL) at rt was added dropwise a solution of ceric ammonium nitrate (1.64 g, 3.00 mmol) in 1.5 mL water. The reaction was stirred for 5 min and then diluted with EtOAc (20 mL). The resultant solution was washed sequentially with water (20 mL), 5% $NaHCO_3$ (2× 20 mL), 5% $NaHSO_3$ (2× 20 mL) and brine (20 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated, and the residue was chromatographed on silica gel (1:2 EtOAc/hexanes) to give 0.172 g (75%) of **25a** as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.10–7.50 (m, 4H), 5.10 (1H, d, J = 1.5 Hz), 4.49 (1H, d, J = 2.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 164.7, 134.7, 132.9, 129.9, 129.8, 127.3, 126.2, 63.4, 59.7.

An analogous procedure was used to prepare compounds **25b–c**, **29a–d**, **32a–c**, **36a–c**, and **41a–g**.

4.30. (±)-(3*S*,4*S*)-4-(2-Chlorophenyl)-3-iodoazetidin-2-one (25b)

Yellow oil in 72% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.50 (1H, m), 7.10–7.30 (4H, m), 6.50 (1H, br s), 5.62(1H, d, J = 2.5 Hz), 5.26 (1H, d, J = 2.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 166.0, 135.9, 132.9, 129.8, 127.3, 126.8, 125.9, 59.6, 21.8.

4.31. (±)-(3*S*,4*S*)-3-Azido-4-(2-chlorophenyl)azetidin-2-one (25c)

Yellow oil, ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38–7.19 (4H, m), 6.20 (1H, br s), 4.90 (1H, d, J = 1.8 Hz), 4.33 (1H, d, J = 1.8 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.1, 142.3, 132.2, 128.4, 128.2, 128.0, 126.7, 64.2, 44.3.

4.32. (±)-(3*S*,4*S*)-4-(2-Chlorophenyl)-3-propylaminoazetidin-2-one (29a)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.88 (1H, br s), 7.31–7.12 (4H, m), 4.73 (1H, d, J = 6.5 Hz), 4.49 (1H, d, J = 6.4 Hz), 3.83 (1H, br s), 1.84 (4H, m), 1.43 (4H, m); ^{13}C NMR (63 MHz, $CDCl_3$): δ 179.5, 140.4, 133.2, 130.4, 129.5, 129.2, 127.6, 55.4, 42.7, 42.5, 33.3, 33.2, 27.9, 27.6.

4.33. (±)-(3*S*,4*S*)-3-Benzylamino-4-(2-chlorophenyl)azetidin-2-one (29b)

86% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.78 (1H, br s), 7.33–7.16 (9H, m), 4.53 (1H, d, J = 6.3 Hz), 4.42 (1H, d, J = 6.1 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 187.6, 160.0, 137.0, 134.7, 130.4, 130.3, 130.1, 130.0, 129.7, 129.6, 129.2, 128.3, 127.6, 55.7, 51.8, 43.6.

4.34. (±)-(3*S*,4*S*)-4-(2-Chlorophenyl)-3-diethylaminoazetidin-2-one (29c)

80% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.62 (1H, br s), 7.28–7.19 (4H, m), 4.75 (1H, d, J = 5.2 Hz), 4.49 (1H, d, J = 5.2 Hz), 3.18 (2H, q, J = 7.1 Hz), 3.09 (2H, q, J = 7.2 Hz), 1.15 (6H, t, J = 7.1 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 165.9, 134.2, 132.2, 131.1, 129.7, 129.4, 127.5, 55.8, 49.3, 42.3, 37.8, 14.0, 12.2.

4.35. (±)-(3*S*,4*S*)-4-(2-Chlorophenyl)-3-diisobutylaminoazetidin-2-one (29d)

78% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.31–7.20 (4H, m), 6.96 (2H, d, J = 8.8 Hz), 6.65 (2H, d, J = 8.8 Hz), 4.98 (2H, s), 3.68 (3H, s), 2.90 (4H, t, J = 6.6 Hz), 1.90 (1H, m), 1.45 (1H, m), 0.76 (6H, d, J = 6.6 Hz), 0.35 (6H, d, J = 6.6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 163.1, 136.9, 135.2, 134.1, 130.2, 129.4 127.5, 71.9, 56.2, 55.0, 41.6, 28.3, 26.8, 20.6, 20.5, 20.3, 20.2.

4.36. (±)-(3*R*,4*S*)-3-Allyloxy-4-(2-chlorophenyl)-azetidin-2-one (32a)

Brown semi-solid 69% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.50–7.26 (4H, m), 6.25 (1H, br s), 5.70–5.55 (1H, m), 5.26 (1H, d, J = 4.6 Hz) 5.11–4.99 (2H, m), 4.97 (1H, d, J = 4.6 Hz), 3.93–3.89 (2H, m); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.7, 133.8, 133.2, 129.1, 128.4, 126.9, 117.8, 84.6, 71.8, 56.0.

4.37. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-3-propoxyazetidin-2-one (32b)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.49 (1H, d, J = 1.9 Hz), 7.46–7.27 (3H, m), 6.30 (1H, br s), 5.26 (1H, d, J = 4.5 Hz) 4.91 (1H, d, J = 4.5 Hz), 3.47–3.38 (1H, m), 3.25–3.19 (1H, m), 1.33–1.24 (2H, m), 0.54 (3H, t, J = 7.4 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.6, 133.9, 133.0, 129.2, 129.0, 128.4, 126.8, 85.8, 73.1, 56.1, 22.6, 10.0.

4.38. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-3-methoxymethoxy-azetidin-2-one (32c)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.48–7.26 (4H, m), 6.26 (1H, br s), 5.29 (1H, d, J = 5.0 Hz), 5.17 (1H, d, J = 5.0 Hz), 4.55 (2H, s), 3.21 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 169.3, 133.3, 129.9, 128.7, 128.5, 127.7, 126.8, 96.1, 84.2, 57.3, 50.2.

4.39. (±)-(3*R*,4*S*)-3-Methylsulfonyl-4-phenylazetidin-2-one (36a)

Yellow oil in 90% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.36–7.19 (5H, m), 6.58 (1H, br s), 5.71 (1H, d, J = 4.9 Hz), 4.99 (1H, d, J = 4.9 Hz), 2.68 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 164.7, 134.2, 129.6, 129.1, 128.7, 128.5, 127.8, 81.7, 58.2, 39.2.

4.40. (±)-(3*R*,4*S*)-3-Benzenesulfonyl-4-phenylazetidin-2-one (36b)

Yellow oil, 88% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.05 (1H, d, J = 8.0 Hz), 7.78–7.63 (6H, m), 7.48–7.20 (3H, m), 6.42 (1H, br s), 5.83 (1H, d,J = 4.8 Hz), 5.41 (1H, d, J = 4.8 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 164.2, 136.0, 134.5, 134.3, 129.6, 129.2, 128.9, 128.5, 128.2, 128.1, 127.3, 127.1, 116.5, 81.5, 58.4.

4.41. (±)-(3*R*,4*S*)-4-Phenyl-3-(4-toluenesulfonyl)azetidin-2-one (36c)

Yellow oil, 85% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.45–7.18 (9H, m), 6.41 (1H, br s), 5.69 (1H, d, J = 2.4 Hz), 4.95 (1H, d, J = 4.7 Hz), 2.41 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 164.3, 136.1, 134.6, 134.4, 130.0, 129.3, 129.0, 128.5, 128.3, 128.2, 126.6 (2C), 125.1 (2C), 81.6, 58.5.

4.42. (±)-(3*R*,4*S*)-3-Allyloxy-4-(2-chlorophenyl)-3-methylazetidin-2-one (41a)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.48–7.26 (4H, m), 6.25 (1H, br s), 5.39–5.35 (1H, m), 4.97 (1H, s), 4.86–4.78 (2H, m), 3.82–3.79 (2H, m), 1.80 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.5, 134.5, 133.7, 133.1, 129.2, 128.8, 127.8, 126.6, 116.0, 90.8, 66.8, 62.6, 20.1.

4.43. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-3-methyl-3-propyloxyazetidin-2-one (41b)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.46–7.27 (4H, m), 6.65 (1H, br s), 4.93 (1H, s), 3.25–3.15 (2H, m), 1.74 (3H, s), 1.18–1.04 (2H, m), 0.47 (3H, t, J = 7.4 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.2, 133.2, 130.3, 129.0, 127.1, 126.5, 126.2, 89.8, 63.2, 22.5, 19.2, 10.2.

4.44. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-3-methoxymethoxy-3-methylazetidin-2-one (41c)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.44–7.22 (4H, m), 6.71 (1H, br s), 4.93 (1H, s), 4.52 (2H, s), 3.05 (3H, s), 1.80 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.2, 134.7, 133.1, 129.2, 128.9, 127.8, 126.7, 93.0, 89.8, 62.6, 55.6, 20.3.

4.45. (±)-(3*R*,4*S*)-3-Acetoxy-4-(2-chlorophenyl)-3-methyl-azetidin-2-one (41d)

Brown oil, 94% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.49–7.18 (4H, m), 5.00 (1H, s), 1.86 (3H, s), 1.54 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 169.4, 168.4, 133.2, 133.1, 129.0, 128.8, 126.4, 88.1, 62.2, 29.6, 20.1.

4.46. (±)-(3*R*,4*S*)-3-Acetoxy-4-(2-chlorophenyl)-3-(2-propen-yl)azetidin-2-one (41e)

Brown oil, 35% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.51–7.37 (1H, m), 7.36–7.23 (3H, m), 7.02 (1H, br s), 5.99–5.92 (1H, m), 5.37–5.25 (2H, m), 5.13 (1H, d, J = 1.5 Hz), 2.99 (2H, d, J = 7.3 Hz), 1.58 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.2, 163.4, 156.4, 133.9, 130.8, 129.9, 129.4, 126.4, 120.9, 118.5, 114.3, 88.3, 55.3, 37.5, 20.1.

4.47. (±)-(3*R*,4*S*)-3-Acetoxy-4-(2-chlorophenyl)-3-propylazetidin-2-one (41f)

Brown oil, 91% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.48–7.18 (4H, m), 6.65 (1H, s), 5.01 (1H, s), 2.35–2.11 (2H, m), 1.72–1.50 (2H, m), 1.58 (3H, s), 1.57 (3H, s), 0.98 (3H, t, J = 7.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 169.1, 168.6, 133.2, 133.1, 129.1, 128.9, 126.4, 115.9, 90.0, 60.6, 36.1, 20.0, 16.6, 14.1.

4.48. (±)-(3*R*,4*S*)-3-Acetoxy-4-(2-chlorophenyl)-3-phenylazetidin-2-one (41g)

Brown oil, 95% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.75 (2H, d, J = 7.1 Hz), 7.36–7.23 (3H, m), 7.02 (1H, br s), 5.99–5.92 (1H, m), 5.37–5.25 (2H, m), 5.13 (1H, d, J = 1.5 Hz), 2.99 (2H, d, J = 7.3 Hz), 1.58 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.0, 167.7, 134.8, 133.9, 133.1, 129.4, 129.2, 128.9, 128.8, 128.5, 126.4, 126.0, 91.6, 61.9, 20.3.

4.49. Synthesis of (±)-(3*S*,4*S*)-3-chloro-4-(2-chlorophenyl)-*N*-methylthioazetidin-2-one (19a)

To a solution of **25a** (0.027 g, 0.13 mmol) in benzene were added *N*-methylthiophthalimide (0.025 g, 0.133 mmol) and 1 drop of triethylamine. The mixture was refluxed overnight and washed with 1% KOH. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (1:4 EtOAc/hexanes) to yield 0.021 g (71%) of **19a** as a brown oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.20–7.40 (4H, m), 5.10 (1H, d, J = 1.5 Hz), 4.60 (1H, d, J = 2.0 Hz), 2.50 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 166.0, 131.2, 130.4, 128.5, 127.2, 66.2, 62.5, 20.6.

An analogous procedure was used to prepare compounds **19b–c**, **26a–d**, **30a–c**, **33a–c**, **37a–g**, **43a–b**, **43f–j**, **43l**, **43n**, and **43q–t**.

4.50. (±)-(3*S*,4*S*)-4-(2-Chlorophenyl)-3-iodo-*N*-methylthioazetidin-2-one (19b)

Brown oil, 86% yield ^{1}H NMR (250 MHz, $CDCl_3$) δ (1H, d, J = 3.5 Hz), 7.39–7.36 (2H, m), 7.10–7.20 (1H, m), 5.60 (1H, d, J = 2.5 Hz), 5.30 (1H, d, J = 2.5 Hz), 2.58 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.6, 134.2, 133.8, 130.2, 127.5, 127.1, 126.7, 66.4, 21.4, 20.3.

4.51. (±)-(3*S*,4*S*)-3-Azido-3-(2-chlorophenyl)-*N*-methylthioazetidin-2-one (19c)

Yellow solid, 83% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.35–7.19 (4H, m), 5.74 (1H, d, J = 1.8 Hz), 4.95 (1H, d, J = 1.8 Hz), 2.37 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.2, 142.5, 133.5, 128.9, 128.7, 128.2, 128.0, 60.8, 52.2, 20.8.

4.52. (±)-(3*S*,4*S*)-*N*-Methylthio-3-propylaminoazetidin-2-one (26a)

68% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.33–7.16 (4H, m), 4.51 (1H, d, J = 6.4 Hz), 3.84 (1H, br s), 2.41 (3H, s), 1.85 (4H, m), 1.47 (4H, m); ^{13}C NMR (63 MHz, $CDCl_3$): δ 189.5, 140.2, 133.2, 130.4, 129.5, 127.6, 127.4, 48.8, 47.7, 42.7, 33.3, 33.2, 27.8, 27.7, 20.2.

4.53. (±)-(3*S*,4*S*)-3-Benzylamino-*N*-methylthioazetidin-2-one (26b)

64% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.25–7.05 (6H, m), 6.61 (3H, m), 4.53 (1H, d, J = 6.3 Hz), 4.42 (1H, d, J = 6.1 Hz), 2.41 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 187.5, 160.0, 137.0, 134.7, 130.4, 130.3, 130.1, 130.0, 129.7, 129.6, 129.2, 128.3, 127.6, 55.7, 51.8, 43.6, 19.4.

4.54. (±)-(3*S*,4*S*)-3-Diethylamino-*N*-methylthioazetidin-2-one (26c)

54% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.62 (1H, br s), 7.28–7.19 (4H, m), 4.75 (1H, d, J = 5.2 Hz), 4.49 (1H, d, J = 5.2 Hz), 3.18 (2H, q, J = 7.1 Hz), 3.09 (2H, q, J = 7.2 Hz), 2.41 (3H, s), 1.15 (6H, t, J = 7.1 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 175.2, 134.5, 129.2, 128.9, 128.7, 128.2, 127.8, 60.8, 54.2, 48.6, 26.2, 25.8, 20.8, 11.4, 11.3.

4.55. (±)-(3*S*,4*S*)-3-Diisobutylamino-*N*-methylthioazetidin-2-one (26d)

48% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.28–7.13 (4H, m), 4.48 (2H, d, J = 6.2 Hz), 3.59 (2H, d, J = 7.5 Hz), 3.13 (2H, d, J = 7.5 Hz), 1.99 (1H, m) 1.96 (1H, m), 0.81 (12H, m); ^{13}C NMR (63 MHz, $CDCl_3$):

δ 173.1, 140.2, 136.9, 130.2, 129.4 127.5, 127.2, 49.9, 48.2, 41.6, 41.3, 39.2, 27.3, 26.8, 23.5, 23.4, 20.2.

4.56. (±)-(3*R*,4*S*)-3-Allyloxy-4-(2-chlorophenyl)-*N*-methylthioazetidin-2-one (30a)

25% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.39 (1H, d, J = 5.8 Hz), 7.38–7.27 (3H, m), 5.62–5.51 (1H, m), 5.34 (1H, d, J = 4.8 Hz), 5.06 (2H, d, J = 11.6 Hz), 4.99 (1H, d, J = 4.8 Hz), 3.93–3.78 (2H, m), 2.45 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.4, 133.7, 132.8, 131.6, 129.5, 129.4, 129.1, 126.7, 118.0, 84.4, 71.6, 62.8, 21.7.

4.57. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-*N*-methylthio-3-propoxyazetidin-2-one (30b)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.34 (1H, d, J = 3.6 Hz), 7.27–7.24 (3H, m), 5.32 (1H, d, J = 4.8 Hz), 4.91 (1H, d, J = 4.8 Hz), 3.38–3.32 (1H, m), 3.09–3.04 (1H, m), 2.42 (3H, s), 1.27–1.19 (2H, m), 0.49 (3H, t, J = 7.5 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.5, 134.6, 133.8, 131.6, 129.4, 129.1, 126.6, 85.6, 72.9, 63.0, 22.4, 21.8, 10.0.

4.58. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-3-methoxymethoxy-*N*-methylthioazetidin-2-one (30c)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.39 (1H, d, J = 5.2 Hz), 7.38–7.26 (3H, m), 5.37 (1H, d, J = 5.1 Hz), 5.19 (1H, d, J = 5.1 Hz), 4.51 (1H, d, J = 6.6 Hz), 3.14 (3H, s), 2.47 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.6, 134.6, 131.8, 129.5, 129.4, 128.8, 126.8, 96.3, 82.2, 62.8, 55.7, 21.7.

4.59. (±)-(3*R*,4*S*)-3-Methylsulfonyl-*N*-methylthio-4-phenylazetidin-2-one (33a)

Yellow solid in 72% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.47–7.26 (5H, m), 5.91 (1H, d, J = 5.3 Hz), 5.54 (1H, d, J = 5.3 Hz), 2.96 (3H, s), 2.53 (3H, s); ^{13}C NMR (63 MHz): δ 165.7, 133.2, 129.4, 129.0, 128.7, 127.4, 126.0, 79.9, 60.9, 38.0, 20.9.

4.60. (±)-(3*R*,4*S*)-3-Benzenesulfonyl-*N*-methylthio-4-phenylazetidin-2-one (33b)

Yellow oil, 55% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.64–7.57 (3H, m), 7.45–7.39 (2H, m), 7.30–7.21 (5H, m), 5.85 (1H, d, J = 5.1 Hz), 5.46 (1H, d, J = 5.1 Hz), 2.43 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 165.2, 134.5, 133.5, 133.2, 129.2, 128.9, 128.7, 128.2, 128.0, 127.8, 127.6, 126.7, 125.8, 80.0, 60.8, 20.8.

4.61. (±)-(3*R*,4*S*)-*N*-(Methylthio)-4-phenyl-3-(4-toluenesulfonyl)azetidin-2-one (33c)

Yellow solid, mp 85–87 °C, 74% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.41–7.26 (5H, m), 7.19–7.15 (4H, m), 5.74 (1H, d,J = 5.0 Hz), 4.88 (1H, d, J = 5.0 Hz), 2.40 (3H, s), 2.35 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 166.4, 145.3, 132.4, 132.0, 129.8, 129.2, 129.0, 128.5, 127.8 (2C), 126.8 (2C), 80.6, 66.0, 22.1, 21.7.

4.62. (±)-(3*R*,4*S*)-3-Allyloxy-4-(2-chlorophenyl)-3-methyl-*N*-methylthioazetidin-2-one (37a)

26% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.26 (4H, m), 5.41–5.34 (1H, m), 5.05 (1H, s), 4.84–4.77 (2H, m), 3.83–3.75 (2H, m), 2.48 (3H, s), 1.73 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 169.7, 133.8, 129.7, 129.5, 128.9, 126.9, 116.4, 85.6, 69.5, 67.1, 21.5, 19.1.

4.63. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-3-methyl-*N*-methylthio-3-propoxyazetidin-2-one (37b)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.36–7.28 (4H, m), 4.51 (1H, s), 3.33–3.29 (1H, m), 3.04–3.01 (1H, m), 2.40 (3H, s), 1.61 (3H, s), 1.23–1.14 (2H, m), 0.59 (3H, t, J = 7.4 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.8, 133.4, 130.4, 129.2, 127.3, 126.9, 126.4, 88.5, 64.1, 23.0, 19.5, 16.1, 10.2.

4.64. (±)-(3*R*,4*S*)-4-(2-Chlorophenyl)-3-methoxymethoxy-3-methyl-*N*-methylthioazetidin-2-one (37c)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.36-7-.18 (4H, m), 4.98 (1H, s), 4.46 (2H, s), 3.01 (3H, s), 2.43 (3H, s), 1.72 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.1, 134.2, 130.4, 128.6, 128.4, 127.9, 126.9, 96.3, 85.1, 57.8, 51.2, 20.0, 16.2.

4.65. (±)-(3*R*,4*S*)-3-Acetoxy-4-(2-chlorophenyl)-3-methyl-*N*-methylthioazetidin-2-one (37d)

Yellow oil in 40% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.39–7.38 (1H, m), 7.26 (3H, s), 5.15 (1H, s), 2.49 (3H, s), 1.85 (3H, s), 1.57 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 171.1, 168.1, 134.3, 131.2, 129.5, 129.4, 128.9, 126.3, 88.1, 68.9, 21.3, 20.1, 19.5.

4.66. (±)-(3*R*,4*S*)-3-Acetoxy-4-(2-chlorophenyl)-*N*-methylthio-3-(2-propenyl)azetidin-2-one (37e)

Yellow oil, 33% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.37 (1H, m), 7.26 (3H, br s), 5.93–5.27 (2H, m), 5.30 (1H, s), 3.03-2-.96 (2H, m), 2.48 (3H, s), 1.58 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.0, 168.1, 134.3, 131.2, 129.5, 129.1 126.3, 121.5, 89.9, 65.3, 37.2, 21.8, 20.1.

4.67. (±)-(3*R*,4*S*)-3-Acetoxy-4-(2-chlorophenyl)-*N*-methylthio-3-propylazetidin-2-one (37f)

Yellow oil, 33% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38 (1H, m), 7.27 (3H, m), 5.19 (1H, s), 2.50 (3H, s), 2.33–2.10 (2H, m), 1.72–1.46 (2H, m), 1.58 (3H, s), 0.99 (3H, t, J = 7.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.7, 168.3, 134.3, 131.2, 129.5, 91.0, 67.0, 35.6, 21.5, 20.1, 16.7, 14.1.

4.68. (±)-(3*R*,4*S*)-3-Acetoxy-4-(2-chlorophenyl)-*N*-methylthio-3-phenylazetidin-2-one (37g)

Yellow oil, 40% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.73 (2H, d, J = 7.6 Hz), 7.44–7.32 (7H, m), 5.87 (1H, s), 2.51 (3H, s), 1.65 (3H, s); ^{13}C NMR (63 MHz,

$CDCl_3$): δ 169.3, 167.6, 135.3, 134.1, 131.2, 128.9, 129.7, 129.1, 129.0, 128.6, 126.8, 126.3, 91.8, 67.2, 21.8, 20.3.

4.69. (±)-(3*R*,4*S*)-4-(3-Chlorophenyl)-3-methoxyazetidin-2-one (43a)

White solid; mp 110–111 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30–7.20 (4H, m), 6.58 (1H, brs), 4.76 (1H, d, J = 4.5 Hz), 4.69–4.67 (1H, m), 3.13 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.1, 137.9, 129.6, 128.5, 127.7, 125.8, 86.7, 58.3, 57.6.

4.70. (±)-(3*R*,4*S*)-4-(4-Chlorophenyl)-3-methoxy-*N*-methylthioazetidin-2-one (43b)

White crystals; mp 62–66 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.33 (2H, d, J = 8.5 Hz), 7.25 (2H, d, J = 8.5 Hz), 4.73 (2H, s), 3.13 (3H, s), 2.31 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.2, 134.9, 130.2, 128.6, 86.5, 65.5, 58.4, 22.1.

4.71. (±)-(3*R*,4*S*)-4-(2-Iodophenyl)-3-methoxy-*N*-methylthioazetidin-2-one (43f)

White crystals; mp 62–65 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.80 (1H, d, J = 7.8 Hz), 7.30 (1H, t, J = 7.5 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.00 (1H, t, J = 7.5 Hz), 5.09 (1H, d, J = 5.0 Hz), 4.80 (1H, d, J = 4.8 Hz), 3.82 (3H, s), 2.41 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.7, 139.9, 136.2, 130.6, 129.3, 128.6, 99.8, 87.1, 70.4, 59.6, 22.2.

4.72. (±)-(3*R*,4*S*)-4-(3-Iodophenyl)-3-methoxy-*N*-methylthioazetidin-2-one (43g)

White crystals; mp 97–99 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.65 (2H, m), 7.27 (1H, d, J = 7.7 Hz), 7.08 (1H, t, J = 8.0 Hz), 4.73–4.67 (2H, AB m), 3.13 (3H, s), 2.32 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.6, 138.4, 138.2, 136.4, 130.5, 128.5, 94.5, 87.0, 65.8, 58.3, 22.6.

4.73. (±)-(3*R*,4*S*)-4-(4-Iodophenyl)-3-methoxy-*N*-methylthioazetidin-2-one (43h)

White solid; mp 102–105 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.65 (2H, d, J = 8.3 Hz), 7.03 (2H, t, J = 8.3 Hz), 4.70 (2H, app s), 3.10 (3H, s), 2.29 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.1, 137.5, 133.2, 130.7, 94.9, 86.4, 65.6, 58.4, 22.1.

4.74. (±)-(3*R*,4*S*)-4-(2,4-Dichlorophenyl)-3-methoxy-*N*-methylthioazetidin-2-one (43i)

Yellow crystals; mp 102–105 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.37 (s, 1H), 7.28 (1H, d, J = 8.3 Hz), 7.16 (1H, t, J = 8.2 Hz), 5.24 (1H, d, J = 4.6 Hz), 4.97 (1H, d, J = 4.6 Hz), 3.19 (3H, s), 2.40 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.5, 135.3, 134.9, 130.6, 130.3, 129.9, 127.7, 87.1, 62.6, 59.4, 22.2.

4.75. (±)-(3*R*,4*S*)-4-(2,6-Dichlorophenyl)-3-methoxy-*N*-methylthioazetidin-2-one (43j)

Pale yellow solid; mp 77–80 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.23 (1H, t, J = 8.1 Hz), 5.72 (1H, d, J = 5.3 Hz), 4.90 (1H, d, J = 5.1 Hz), 3.30 (3H, s), 2.44 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 168.3, 131.1, 130.1, 128.8, 88.0, 62.9, 59.2, 21.6.

4.76. (±)-(3*R*,4*S*)-3-Methoxy-4-(2-methoxyphenyl)azetidin-2-one (43l)

White solid; mp 120–123 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.27-07.24 (1H, app m), 7.190-7.15 (1H, m), 6.95 (1H, t, J = 7.5 Hz), 6.86 (1H, d, J = 8.2 Hz), 5.27 (1H, d, J = 4.9 Hz), 4.72 (1H, d, J = 4.9 Hz), 3.80 (3H, s), 3.12 (3H, s), 2.37 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.9, 157.7, 129.5, 128.5, 121.5, 120.4, 110.3, 86.5, 60.2, 58.5, 55.4, 21.8.

4.77. (±)-(3*R*,4*S*)-3-Methoxy-*N*-methylthio-4-(2-nitrophenyl)-azetidin-2-one (43n)

Yellow solid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.12 (1H, d, J = 8.2 Hz), 7.66–7.63 (1H, m), 7.50–7.41 (2H, m), 5.49 (1H, d, J = 5.1 Hz), 4.93 (1H, d, J = 5.2 Hz), 3.23 (3H, s), 2.43 (3H, s).

4.78. (±)-(3*R*,4*S*)-3-Methoxy-*N*-methylthio-4-(4-propenyl-oxyphenyl)azetidin-2-one (43q)

White solid; mp 87–88 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.29 (2H, d, J = 8.4 Hz), 7.08 (2H, d, J = 8.4 Hz), 6.50 (1H, d, J = 17.3 Hz), 6.21 (1H, dd, J = 17.1, 10.3 Hz), 5.92 (1H, d, J = 10.4 Hz), 4.75 (1H, d, J = 4.8 Hz), 4.69 (1H, d, J = 4.8 Hz), 3.05 (3H, s), 2.26 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.3, 164.2, 150.9, 132.9, 131.1, 129.9, 127.7, 121.4, 86.5, 65.5, 58.3, 22.0.

4.79. (±)-(3*R*,4*S*)-4-(4-Hydroxyphenyl)-3-methoxy-*N*-methylthioazetidin-2-one (43r)

White solid; mp 119–123 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.18 (2H, d, J = 9.0 Hz), 6.81 (2H, d, J = 9.0 Hz), 5.73 (1H, br s), 4.69 (2H, app s), 3.11 (3H, s), 2.28 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.9, 168.5, 130.4, 124.9, 115.4, 65.9, 58.3, 22.1.

4.80. (±)-(3*R*,4*S*)-4-Biphenyl-3-methoxy-*N*-methylthioazetidin-2-one (43s)

Light yellow solid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.65 (4H, d, J = 6.5 Hz), 7.43–7.34 (5H, m), 4.85 (1H, d, J = 4.3 Hz), 4.81 (1H, d, J = 4.4 Hz), 3.12 (3H, s), 2.33 (3H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 169.5, 142.3, 141.6, 135.8, 129.1, 128.2, 127.5, 127.4, 87.5, 59.1, 58.3.

4.81. (±)-(3*R*,4*S*)-4-Fluorenyl-3-methoxy-*N*-methylthioazetidin-2-one (43t)

Colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.75 (2H, d, J = 7.5 Hz), 7.50 (2H, d, J = 6.6 Hz), 7.34–7.24 (3H,

m), 4.85 (1H, d, $J = 4.9$ Hz), 4.77 (1H, d, $J = 4.9$ Hz), 3.88 (2H, s), 3.14 (3H, s), 2.33 (3H, s).

4.82. Testing of antimicrobial susceptibilities (Kirby–Bauer well diffusion)

Staphylococcus aureus (ATCC 25923) and MRSA (ATCC 43300 and 33591) were purchased from ATCC sources. Eight additional strains of MRSA were obtained from Lakeland Regional Medical Center (Lakeland, FL).

4.83. Culture preparation

From a freezer stock in tryptic soy broth (Difco Laboratories, Detroit, MI) and 20% glycerol, a culture of each microorganism was transferred with a sterile Dacron swab to Trypticase® Soy Agar (TSA) plates (Becton–Dickinson Laboratories, Cockeysville, MD), streaked for isolation, and incubated at 37 °C for 24 h. A 10^8 standardized cell count suspension was then made in sterile phosphate-buffered saline (pH 7.2) and swabbed across fresh TSA plates.

4.84. Antimicrobiological testing

Prior to swabbing with the culture solution, 20 μL of a 1 mg/mL stock solution of the test lactam compound in dimethylsulfoxide (DMSO) was added to a 6-mm diameter well bored into the agar. The plates were swabbed uniformly with the test microbe compound above and then incubated for 24 h at 37 °C. The antimicrobial susceptibilities were determined by measuring the zones of growth inhibition around each well.

4.85. Determination of minimum inhibitory concentrations

The minimum inhibitory concentration (MIC) values of the lactams were determined for *S. aureus* and MRSA by serial dilution, according to NCCLS protocols.[19] The test medium was prepared in 24-well plates (Costar 3524, Cambridge, MA) by adding the test drug in DMSO to Mueller–Hinton II agar (Becton–Dickinson Laboratories, Cockeysville, MD) to bring the total volume in each well to 1.0 mL. Starting with an initial well concentration of 256 μg of drug/mL, each sequential dilution contained half the concentration of the drug. The medium was allowed to solidify at room temperature for 24 h before inoculation with the bacteria. Using a sterilized inoculating loop, a small amount of each standardized *Staphylococcus* strain cultured on TSA plates for 24 h was transferred into sterile test tubes containing 5 mL TSA broth and incubated at 37 °C for 24 h. One microliter of each culture was then applied to the appropriate well of Mueller–Hinton agar and incubated at 37 °C overnight. After 24 h, the MICs were determined as the lowest concentration of the drug where bacterial growth was visibly inhibited.

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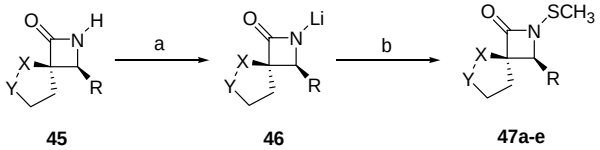

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