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Non-transpeptidase binding arylthioether β -Lactams active against *Mycobacterium tuberculosis* and *Moraxella catarrhalis*

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Abstract

The prevalence of drug resistance in both clinical and community settings as a consequence of alterations of biosynthetic pathways, enzymes or cell wall architecture is a persistent threat to human health. We have designed, synthesized, and tested a novel class of monocyclic β -lactams that carry an arylthio group at C4. These thioethers exhibit inhibitory and cidal activity against serine β -lactamase producing *Mycobacterium tuberculosis* wild type strain (Mtb) and multiple (n=8) β -lactamase producing *Moraxella catarrhalis* clinical isolates.

Keywords

Mycobacterium tuberculosis, *Moraxella catarrhalis*, β -Lactams; Antimicrobial resistance

1. Introduction

The β -lactams are one of the most successful classes of antibiotics. However, they are rapidly losing their effectiveness due to expression of β -lactamases by bacteria. Therefore, new approaches to drug development are needed to target the organisms that are resistant to β -lactam antibiotics. This can be achieved by designing antimicrobials that are resistant to hydrolysis by these enzymes. As previously reported, we synthesized and tested a library of monocyclic β -lactams some of which have antimicrobial activity against two phylogenetically distant β -lactamase producing bacterial species – *Moraxella catharralis* (*M. cat.*) and *Mycobacterium tuberculosis* (Mtb). ¹ The tested compounds were substituted at C4 (Figure 1) with alkylthio- as well as arylthio-groups, with amino-, hydroxy- and sulfhydryl-substituents at the *para* position on the aromatic ring, and their *N*-sulfonates. The most active compounds were type **I** azetidinone thioethers with arylthio group at C4, lacking the

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sulfonate at the lactam nitrogen (Figure 1). *N*-Sulfonation of these lactams (type **II**, Figure 1) did not enhance their antimicrobial activity.¹ Structure-activity relationship (SAR) studies of lactams **I** and **II** (Figure 1) indicate that the presence of the C4-arylthio group is essential for antimicrobial activity. In addition, the N1-substituent also has an important role. Taken together, these data demonstrate that lactams with sulfenated N1, even with a C4-arylthioether, have either comparable or diminished antibacterial activity against Mtb and *M.cat*.¹ The foci of this study were to: 1) determine the antimicrobial activity of compounds in which the sulfur atom at C4 was replaced with an alternative heteroatom, e.g. an oxygen atom; 2) determine the effect of an electron-withdrawing group (EWG) or an electron-donating group (EDG) at the arylthio - substituent at C4 on antimicrobial activity; and 3) identify the optimal functional group at the lactam nitrogen for maximal antimicrobial activity.

2. Chemistry

The overall procedures for generating the various C4-substituted β -lactams are summarized in Scheme 1. The requirement for an arylthio-group at the C4 was determined by synthesis and subsequent antimicrobial testing of compounds having phenoxy- and selenophenoxy-substituents at C4. These compounds were either unsubstituted or carbamylated at N1 (Scheme 1).

The effect on antimicrobial activity of various EWGs or EDGs at different positions on the aromatic ring was determined. This set of compounds, C4-arylthio- β -lactams **2 – 27** (Scheme 1, Table 1) were prepared from 4-acetoxy-2-azetidinone **1** and the corresponding arylthiols, by a procedure described by Clauss *et al.*² and Wasserman *et al.*³ Carbamylation of the lactam nitrogen (lactams **30 – 70**) with a variety of isocyanates was accomplished by adopting a procedure from Mulchande *et al.*³ or by a microwave-based method developed in our laboratory. β -Lactams **37-39, 55, 56, 59-63, 65-68, 70** were prepared in methylene chloride (5 ml) with 1.2 molar equivalents of triethylamine using a CEM microwave apparatus (300W, 30°C for 10-45 minutes). Incubation time varied depending on the nature of isocyanate and the unsubstituted lactam. Lactams **28** and **29** were purchased from Sigma-Aldrich (St. Louis, MO). Lactam **58**, with a terminal triple bond, was prepared by the addition of 5-hexanoic acyl chloride to lactam **2**.⁵

3. Results and Discussion

We recently described the synthesis and characterization of a family of C4-arylthio- β -lactams having antimicrobial activity against Mtb and *M.cat*.¹ The initial library of compounds were either unsubstituted at N1 (**I**, Figure 1) or sulfenated at N1 (**II**, Figure 1). Antimicrobial activity of the compounds unsubstituted at the N1 lactam was either similar, or increased, as compared to the activity of compounds sulfenated at N1. Treatment of β -lactam **2** with benzylisocyanate produced **30**. β -Lactam **30** was significantly more active against both *M.cat*. and Mtb (MICs of 12.5 μ g/ml and 6.25 μ g/ml, respectively). Therefore the addition of a benzylcarbamyl group to the lactam nitrogen resulted in a 16- and 4- fold increase in activity for *M.cat*. and Mtb, respectively (**2** vs. **30**; Table 1). Subsequently, β -lactam ethers having arylthio-groups at C4 with both EWGs and EDGs at *o*-, *m*- and *p*-

positions were synthesized then tested. To determine the compounds with the optimal substituents at C4 and N1, we systematically synthesized and compared the antimicrobial activities of compounds containing a H vs. a carbamyl moiety at N1 (Table 1). β -Lactams **6**, **8-13** and **27** have demonstrated antimicrobial activity against *M.cat.* (MIC 12.5 μ g/ml; MBC 50 μ g/ml). The addition of a carbamyl group at N1 (lactams **30-33**, **35**, **42-44**, Table 1) improved the anti-*M.cat.* activity. Moreover, these lactams exhibit narrow spectrum activity against *M.cat.* and Mtb since these compounds had no effect on β -lactamase-nonproducing quality control Gram positive and Gram negative organisms (Table 4; *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecalis*). In addition, these compounds were not cidal against β -lactamase producing, clinical isolates of *E.coli*, *Citrobacter freundii*, *Klebsiella pneumoniae*, *Stenotrophomonas maltophilia*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Streptococcus faecalis*, and *Pseudomonas aeruginosa* (Table 4; data not shown).

Replacement of the N-carbamyl moiety with a carbonyl group as in lactam **58**, (Table 2) leads to diminished antibacterial activity. This may be the result of the intrinsically high chemical reactivity of the lactam ring in this structure due to the presence of the carbonyl group at N1, resulting in intrinsic chemical degradation prior to cellular uptake. The purification of lactam **58** by column chromatography using silicagel proved difficult due to the ease of opening of the lactam ring.

When considering the effect of the XAr1 group (Scheme 1) on anti-*M.cat.*, and anti-Mtb activity, the most active compounds were those having halogenated aryl moieties on the thioether (X=S) groups at C4. For example, lactams with arylthioether groups at C4 with multiple fluoro- or chloro- groups, regardless of whether the substituent on the lactam nitrogen is a hydrogen or a carbamyl group, exhibit the highest levels of demonstrated activity (Table 1; **6 & 34**; **7 & 35**, **8 & 36**, **9 & 37**, **10 & 38**, **11 & 39**). Interestingly, positioning of the fluorine in di-fluorinated compounds affects antimicrobial activity. Lactam **6** (*ortho* and *para*) exhibits a 16- and 8- fold higher level of cidal activity against *M.cat.* and Mtb, respectively, when compared to compound **7** (*meta* and *para*). We hypothesize that placement of electron withdrawing fluorine atoms at the *ortho*- and *para*-positions relative to the sulfur atom in the thiophenoxy group at C4 decreases the electron density on the S atom at C4 through both resonance and induction. This idea is supported by the findings that the di-fluorinated lactams **6** and **7** have better antimicrobial activity than their mono-fluorinated analogs (lactams **3-5**, Table 1). In contrast, the fluorine at the *meta* position would have decreased electron withdrawal capability. This would have diminished effect on the electron density of the S atom due to weak resonance. This is reflected in differences in antimicrobial activity (**6** and **7**, Table 1). Monofluorinated thiophenoxy groups at C4 alone are insufficient to make the compounds (**3-5**, Table 1) active within the accepted therapeutic range for screening of novel antimicrobials (MBC <35 μ g/ml).⁶ However, the replacement of the proton with a carbamyl group at N1 results in significantly improved antimicrobial activity (compounds **3-5** vs. **31-33**, Table 1). This improvement in antimicrobial activity could be explained by several different mechanisms. It may be that the carbamyl group has “regenerated” the isocyanate within the given microorganism (Scheme 4, mechanism **b**)). Alternatively, it is also plausible that the weak electron-withdrawing effect of the benzyl

carbamyl group increases the electrophilicity of the lactam ring, as compared to its counterpart lacking the carbamyl-group at N1.

To further explore the mechanism by which halogens affect antimicrobial activity, lactams with chlorine-substituted thiophenols were synthesized and tested for antimicrobial activity. When one or both fluorines in the thiophenoxy group at C4 were replaced by chlorine atoms, the lactams demonstrated antimicrobial activity, regardless of the R₂ group (hydrogen **9-11** vs. carbamyl **37-39**). However, substitution of a chlorine for a fluorine, in general, decreases antimicrobial activity of the di-halogenated compounds. Of all di-halogenated compounds tested compound **6** demonstrated the most potent antimicrobial activity as compared to compounds **7, 9, 10**, and **11**. Conversely, the presence of chlorine at the *meta*-position improves the activity of the compound (lactam **10**) as compared to its fluorinated counterpart (lactam **7**). The small but measurable difference in activity between lactams **7** and **10** may be due to the empty 3d orbitals in Cl which can accept π -electrons from the aromatic ring. Fluorines lack energetically accessible empty orbitals for such delocalization.

The effects of CF₃ at various positions relative to the S atom illustrate the diversity of *M.cat.* vs. *Mtb* sensitivity to this library of lactams (Table 1). When considering the antimicrobial activity of compounds **13-16**, lactam **13** demonstrated the best activity against *M.cat.* (MIC 1.5 μ g/ml), while lactams **14** and **15** were more effective against *Mtb* (MIC 6.25-12.5 μ g/ml). When comparing lactams **4** and **14**, the presence of a CF₃ group at the *meta*-position increases the anti-*Mtb* activity. This is likely due to the higher electron-withdrawing power of the CF₃. Hence, the induction of the CF₃ group may decrease even further the electron density of the atom (in this case S) at C4. The presence of one vs. two CF₃ groups at the *meta*-positions (lactam **14** vs. **16**, Table 1), affects the antimicrobial activity against *M.cat.* and *Mtb* but in opposing directions; interestingly, the activity of the corresponding carbamylated **42** and **44** lactams is the best as compared to all compounds tested for both microorganisms (MIC 3.13-6.25 μ g/ml and 6.25-25 μ g/ml, *M. cat* and *Mtb*, respectively). Substitution of another EWG group, *para*-nitro lactam, at the thioether moiety at C4, has activity within therapeutic range (<35 μ g/ml)⁶ for both *Mtb* and *M.cat.*, regardless of the presence or absence of a carbamyl group at N1 (compounds **12** and **40**; Table 1). However, the relatively stable CF₃ compounds are better candidates for clinical use, since there is the potential for reduction of the nitro-group *in vivo* (**12** and **40**, Table 1).

Another cadre of compounds, these with various EDG substituted on the arylthiol, were synthesized and tested. Initially, the effect of one or more methoxy groups at all positions on the thioaryl moiety at C4 on anti-*Mtb* and anti-*M.cat.* activity was determined (compounds **17-21** and **45-49**; Table 1). The methoxy group is an EDG with similar size to the CF₃ group. This group of compounds lacked significant activity, even after carbamylation at N1 (compounds **45-49**). In addition, a lactam with a thionaphtyl group at C4 lacked antimicrobial activity, even after carbamylation (compound **24** vs. **52**). The lack of activity may be attributable to steric limitations for the bulkier thionaphtyl group, or to its weak electron-withdrawing capacity. Compound **23** lacks antimicrobial activity as well, even after carbamylation (**51**). Interestingly, compound **22**, with a 2-thiophenethio-moiety at C4, has modest (*M. cat.*) to good (*Mtb*) antimicrobial activity which is relatively unaffected by carbamylation (lactam **50**).

The antimicrobial activities of lactams with aryl groups substituted at C4, and linked to the lactam ring via an O or Se, were assessed (Scheme 1; compounds **25-27**, **53-55**, Table 1). With the exception of lactams **27** and **53**, none of these aryloxy lactams, even after carbamylation, possess improved antimicrobial activity relative to their C4 arylthiol counterparts (compounds **25** vs. **12**; **26** vs. **15**; **54** vs. **43**; **55** vs. **30**); the absence of a sulfur (or selenium) atom at the phenyl substituent at C4 may account for the lack of activity. Compound **53** has a nitro-substituted phenoxide at C4, while compound **27** has an arylseleno group at C4, and is unsubstituted at N1. Compared to oxygen, sulfur and seleniums are larger and have greater polarizability. This may explain why sulfur and selenium, in thiophenoxy and selenophenoxy – substituted at C4 lactams, respectively, carry a larger share of the charge in the transition state, than does oxygen in analogous oxygen isosters.⁷ Thus, this size/polarizability differential contributes to their better antimicrobial activity. This hypothesis is supported by the bond lengths of C4-X (X=O, S, Se) and the charges at X and C4, respectively (Table 5). Comparing the bond lengths and angles observed in the β -lactams described here to all non-cyclic thio-ethers⁸ found in the Cambridge Structural Database (CSD; over 45,000 compounds some with multiple molecules in the asymmetric unit) showed good agreement (Table 5). For comparison a similar search was done on ethers⁹ which have shorter bond lengths as compared with thioethers (bond angle 116.71° in the ethers vs. 102.37° in the thio-ethers).

The majority of the lactams having phenoxy-substituents at C4 lacked antimicrobial activity at therapeutic levels. However, the selenoxy-substituted lactams (**27** and **55**) were bactericidal, even when lacking an EWG on the aromatic ring. This suggests that the transition states for loss of thiophenoxide and especially for selenophenoxide ions from the thiophenoxy- and selenophenoxy- substituted at C4 lactams most likely take place later than those of comparable phenoxy derivatives. This is the primary factor determining the antimicrobial activity of these compounds (Scheme 1).

The evidence supports two possible mechanisms for reaction of these compounds with nucleophiles (Scheme 2). First, an enzyme having a serine as a nucleophile may hydrolyse the lactam ring, a well documented process (mechanism **a**, Scheme 2).¹⁰⁻¹² Alternatively, it is possible that the lactam moiety plays the role of a thiophenol carrier, with the thiophenol functioning as the microbicidal part of the molecule (mechanism **b**, Scheme 2). Due to the unsubstituted lactam nitrogen the first mechanism is unlikely to involve the active site serine of the transpeptidases, since these lactams lack the necessary prerequisites for binding to transpeptidases or β -lactamases, i.e., a chargeable polar group at the lactam nitrogen. To the best of our knowledge, only one monocyclic β -lactam having a phenylthioether at C4 and carbamylated at N1 has been ever reported to have activity against a pathogen, albeit a virus (human cytomegalovirus protease inhibitor).¹⁰ As expected, none of the compounds herein were hydrolysed by penicillinase.¹¹⁻¹³ However, our compounds were hydrolysed by sodium hydroxide with departure of the thiophenoxide from the lactam.⁷

Another plausible mechanism involves heterolytic cleavage of the N1-C4 bond of the azetidin-2-one and the formation of α,β -unsaturated amide *via* the zwitterionic intermediate (Scheme 3). β -Lactams possessing heteroatoms attached to C4 can undergo N1-C4 cleavage under acidic, basic, and neutral conditions, depending on the nature of the functional groups

at positions 1 and 3.¹⁴⁻¹⁷ Recently, β -lactam ring opening under acidic conditions has been demonstrated with lactams having an aryl substituent at C4.¹⁸ In addition, α,β -unsaturated amides have been reported as transglutaminase inhibitors, based on their function as Michael acceptors to the nucleophilic sulfur in the active site.¹⁹ Regardless of the mechanism, the presence of a EWG will increase the reactivity of the lactam. By increasing the electron deficiency on sulfur prior to departure, the EWG will cause the thioether at C4 to act as a leaving group upon deprotonation of the lactam hydrogen (mechanism **a**, Scheme 2). In the case of the lactam's "classical" enzymatic hydrolysis (mechanism **b**, Scheme 2), or through rearrangement leading to α,β -unsaturated amides (Scheme 3), the presence of the electron withdrawing group(s) will accelerate these reactions.

When N1 is carbamylated, mechanism **b**, Scheme 4 should also be considered in addition to the mechanisms described earlier (mechanism **a**, Scheme 2). As shown in Scheme 4, an isocyanate molecule could also be released, which would generate an electrophile; this in turn can bind to a second nucleophile (similarly to mechanism **b**, Scheme 2).

Based on the hypothesized mechanisms of action, the effect the R₂ substituent at the lactam N1 has on antimicrobial activity was determined. The presence of a benzyl carbamyl group as the R₂ group increases the antimicrobial activity most likely because carbamylation makes the lactam ring more electrophilic (**2** vs **30**; **3-5** vs. **31-33**; **15-16** vs. **43-44**, Table 1). However, the cumulative effect of the EWG at C4 and the benzyl carbonyl group at N1 did not always correlate with increased antimicrobial activity (**6** vs. **34**; **8-11** vs. **36-39**; **27** vs. **55**, Table 1). Data indicate that if the electron-withdrawing ability of the substituent at C4 is sufficient for therapeutic levels of activity, carbamylation at N1, in general, did not increase activity. Similarly, placing an EWG at the arylthio moiety of the benzylcarbamyl group yielded a comparable pattern. However, if the substituent at C4 lacked sufficient electron-withdrawing capacity for the compound to be active, then the substituent at N1 contributed to the activity. This is most likely the result of increased electrophilicity of the lactam ring.

Next compounds with alternate EWG at N1 and minimal electron withdrawing capacity at C4 were tested for antimicrobial activity. Compounds with EWGs on the N1-carbamyl demonstrated different antimicrobial activities for *M.cat* vs. *Mtb*. In general, the introduction of a benzyl carbamyl group at N1 of the lactam demonstrated better activity than phenyl- or naphthyl- and even larger carbamyl groups at the N1 (Table 2; **30** vs. **58-63**). Several of these lactams were chemically unstable (compounds **58**, Table 2; **68** and **69**, Table 3); therefore, the optimal substitution remains the benzyl carbamyl group (Table 1). Placing an EDG on the arylthio moiety of the benzyl carbamyl group at N1 does not alter the activity of this compound, as compared to its benzylcarbamylated counterpart (**67** vs. **34**, Table 3).

Summary.

The synthesis and characterization of C4-arylthio- β -lactams carbamylated at N1 as a new family of antibacterial agents active against β -lactamase producing *Mtb* and *M.cat*. has been described. While the presence of a carbamyl substituent at N1 enhances activity, its presence is not necessary if there are EWGs on the arylthioether moiety at C4. The incorporation of EWGs vs. EDGs in the aromatic ring of the arylthio group at C4 led to the observation that

F, Cl, and CF₃ substituents at *ortho* and/or *para* positions, in addition to di-substituted compounds at these positions, possess antibacterial activity within therapeutic range for novel compounds. The replacement of the urea moiety at N1 with a carbonyl group, or replacement of the aromatic ring at C4 with an allyl group demonstrated diminished antibacterial activity. Overall, this library of lactams likely has a different mechanism of action, as compared to the β -lactams in current use. This hypothesis is based on the lack of prerequisite groups for binding to the transpeptidase enzymes and on our mechanistic investigations indicating that these lactams are not substrates of the β -lactamases. Studies are ongoing to optimize the design and synthesis of the present series of C4-arylthio-, N1-carbamylated β -lactams.

4. Experimental

4.1. General Chemistry Methods.

All air- or moisture-sensitive reactions were performed under argon or nitrogen atmosphere using glassware that was pre-dried in an oven at 120 °C overnight. Irradiation reactions were performed in Discover LabMate from CEM (Weddington, NC). The reactions were monitored by thin-layer chromatography (TLC) using EM Reagent plates with fluorescence indicator (SiO₂-60, F₂₅₄) and layer thickness: 350 250 μ m; purchased from EMD Chemicals, Inc. (Gibbstown, NJ). Unless otherwise noted, the compounds were detected under UV light (254 nm) and iodine vapors.

General methods of purification of compounds involved flash chromatography by gradient elution from silica gel columns (60 Å, particle size 40–75 μ m, Sorbent Technologies, Inc., Atlanta, GA), preparatory chromatography plates (silica G prep TLC plates with UV254, 20×20nm glass backed, 1000 μ m thickness, Sorbent Technologies, Inc., Atlanta, GA) and/or recrystallization.

All compounds were characterized by ¹H and ¹³C NMR spectra (25 °C) were obtained at 400 MHz for ¹H NMR and 125 MHz for ¹³C NMR with a Bruker 400 spectrometer (Billerica, MA) in CDCl₃ or acetone-d₆. Chemical shifts are reported in ppm (δ) relative to the residual solvent peak in the corresponding spectra; chloroform d 7.26 and d 77.23 and acetone d 2.05 coupling constants (*J*) are reported in hertz (Hz) (where, s = singlet, br = broad singlet, d = doublet, dd = double doublet, bd = broad doublet, ddd = doublet doublet of doublet, t = triplet, dt = doublet of triplet, q = quartet, p = pentet, m = multiplet). In most cases, signals due to exchangeable protons have been omitted.

IR spectra were obtained as a thin film on NaCl plates and in solid form (KBr standard) on a Shimadzu FT-IR-8300 (Columbia, MD). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Melting points were determined using a TA Instruments Q-2000 Differential Scanning Calorimeter (New Castle, DE) connected to a Refrigerated Cooling System. 3.0 mg $\pm$ 0.2 mg samples were placed in T-Zero aluminum pans with lids and were heated and cooled at a scan rate of 10 °C/min while purged with 50 mL/min N₂. Many of the compounds did not

recrystallize, so temperatures during the first heating scan were reported. The reported temperatures have an uncertainty of $2\sigma = \pm 1.0^\circ\text{C}$.

All anhydrous solvents, reagent grade solvents for chromatography and starting materials were purchased from Sigma-Aldrich (St. Louis, MO), Fisher Scientific (Pittsburgh, PA), Aldrich Chemical Co. (Milwaukee, WI), Matrix Scientific (Columbia, SC) and Acros Organics (Geel, Belgium). Unless stated otherwise, solutions in organic solvents were dried with anhydrous magnesium sulfate, 370 and concentrated under vacuum conditions using rotator evaporation. Abbreviations: DCM = dichloromethane; DMF = dimethylformamide; ACN = acetonitrile; EtOAc = ethyl acetate. All compounds are >98% pure by elemental analysis and MIC values reported are the average of three individual measurements.

General procedure for synthesis of β -lactams containing aromatic thiols, phenol and benzeneselenol.—The synthetic procedure was adopted from Grimm *et al.*² and Wasserman *et al.*³ and applied to our compounds **2–28**. To a solution of 4-acetoxy-2-azetidinone **1** (1 g, 8 mmol) in 50 mL acetone/water (3:2) and 1.05 mol eq. of the corresponding substituents (thiophenols, phenol or benzeneselenol, respectively) was added. Sodium bicarbonate (4 mol eq.) was added and the mixture was stirred vigorously for 12h in a closed round bottom flask. Sodium chloride was added to the solution and after formation of two layers the mixture was filtered out and extracted with EtOAc (3×50 mL). The combined organic layers were dried over MgSO_4 and concentrated under vacuum. The crude product was purified by prep HPLC analysis, flash chromatography and/or re-crystallized.

4-Phenylsulfanyl-azetidin-2-one (2).—The crude product was crystallized from CH_2Cl_2 and hexanes to afford white crystals (62%) with mp. $66\text{--}68^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.42 (5H, m), 6.1 (1H, br), 5.02 (1H, dd, $J=2.3, 4.9$), 3.38 (1H, ddd, $J=1.9, 4.9, 15.2$), 2.9 (1H, ddd, $J=1.5, 2.3, 15.2$); ^{13}C NMR (125 MHz, CDCl_3) δ 165.56, 133.60, 131.21, 129.43, 128.76, 54.20, 45.40. IR (neat) ν_{max} (C=O): 1766.7 cm^{-1} ; *Anal.* calcd for $\text{C}_9\text{H}_9\text{NOS}$; C, 60.31; H, 5.06; N, 7.81. Found: C, 60.26; H, 5.04; N, 7.81.

4-(2-Fluoro-phenylsulfanyl)-azetidin-2-one (3).—Purified by flash chromatography from ethyl acetate/hexanes to give 65% yield and m.p. 101.83°C ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.30 (5H, m), 6.16 (1H, br, s), 4.99 (1H, dd, $J=2.30, 2.66$), 3.36 (1H, ddd, $J=1.85, 3.12, 8.48$), 2.87 (1H, dd, $J=1.38, 13.86$); ^{13}C NMR (125 MHz, CDCl_3) δ 165.75, 164.02, 161.57, 136.30, 131.40, 125.06, 116.62, 54.44, 46.04; IR (neat) ν_{max} (C=O) 1750 cm^{-1} ; X-ray analyses

4-(3-Fluoro-phenylsulfanyl)-azetidin-2-one (4).—Purified by flash chromatography from ethyl acetate/hexanes to give 65% yield. and m.p. 60.94°C ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.30 (5H, m), 6.16 (1H, br, s), 4.99 (1H, dd, $J=2.30, 2.66$), 3.36 (1H, ddd, $J=1.85, 3.12, 8.48$), 2.87 (1H, dd, $J=1.38, 13.86$); ^{13}C NMR (125 MHz, CDCl_3) δ 165.95, 130.93, 128.60, 119.92, 119.70, 115.88, 115.67, 54.21, 45.81; IR (neat) ν_{max} (C=O) 1750 cm^{-1} ; *Anal.* calcd for $\text{C}_{17}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_2\text{S}$; C, 58.61; H, 4.05; N, 8.04. Found: C, 55.00; H, 3.99; N, 7.07.

4-(4-Fluoro-phenylsulfanyl)-azetidin-2-one (5).—Purified by flash chromatography from ethyl acetate/hexanes to give 70% yield. and m.p. 76.67°C ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.01–7.52 (4H, m), 6.11 (1H, br, s), 4.96 (1H, dd, $J=2.19, J=2.66$), 3.37 (1H, ddd, $J=1.82, 3.02, 8.58$), 2.87 (1H, d, $J=15.27$); ^{13}C NMR (125 MHz, CDCl_3) δ , 166.73, 164.70, 162.21, 136.63, 126.13, 116.59, 116.81, 54.78, 45.28; IR (neat) ν_{max} (C=O) 1750 cm^{-1} . X-ray analysis.

4-(2,4-Difluoro-phenylsulfanyl)-azetidin-2-one (6).—Purified by recrystallization in ethyl acetate/hexanes to give 70% yield with m.p. 70–73°C. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.52 (1H, ddd, $J=2.17, 5.30, 6.29$), 7.29 (1H), 6.91–6.98 (3H, m), 6.13 (1H, br, s), 4.96 (1H, ddd, $J=0.44, 1.84, 2.156$), 3.42 (1H, dd, $J=1.86, 3.10, 8.531$), 2.29 (1H, dt, $J=1.88, 11.62$), 1.6 (1H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 166.43, 165.01, 164.37, 162.50, 161.90, 113.36, 112.31, 104.88, 54.38, 45.55; IR (neat) ν_{max} (C=O) 1750 cm^{-1} ; *Anal.* calcd for $\text{C}_9\text{H}_7\text{F}_2\text{NOS}$; C, 50.23 ; H, 3.28 ;N, 6.51. Found: C, 50.32; H, 3.30; N, 6.35.

4-(3,4-Difluoro-phenylsulfanyl)-azetidin-2-one (7).—Purified by recrystallization in ethyl acetate/hexanes to give 47.1% yield with m.p. 74–77°C. ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.11–7.37 (3H, m), 6.17 (1H, br, s), 5.70 (1H, dd, $J=1.39, 2.70$), 5.00 (1H, dd, $J=2.33, 2.64$), 3.64 (1H, ddd, $J=1.74, 2.31, 9.62$), 3.44 (1H, ddd, $J=2.13, 2.85, 8.215$), 3.3 (1H, dt, $J=1.42, 12.64$), 2.90 (1H, dd, $J=1.3, 11.72$), 2.2 (1H, s), 1.6 (1H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 166.53, 152.39, 151.87, 149.89, 149.07, 130.77, 127.39, 123.23, 118.33, 54.70, 45.45; IR (neat) ν_{max} (C=O) 1750 cm^{-1} ; *Anal.* calcd for $\text{C}_9\text{H}_7\text{F}_2\text{NOS}$; C, 50.23; H, 3.28; N, 6.51. Found: C, 50.15; H, 3.26; N, 6.45.

4-Pentafluorophenylsulfanyl-azetidin-2-one (8).—Purified by recrystallization in ethyl acetate/hexanes to give 46% yield with m.p. 80–82°C. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.21 (s, 1H), 6.75 (1H, s), 4.91 (1H, d, $J=3.01$), 3.40 (1H, ddd, $J=1.49, 3.28, 10.84$), 2.92 (1H, dd, $J=15.52, 10.32$), 2.05 (1H, t, $J=26.57$), 1.18 (1H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 165.81, 148.98, 146.59, 143.64, 139.05, 136.65, 110.26, 104.94, 73.01, 54.63, 46.26,

44.73, 30.78, 29.65, 20.6; IR (neat) $\nu_{\max}$ (C=O) 1755 cm^{-1} ; *Anal.* calcd for $\text{C}_9\text{H}_4\text{F}_5\text{NOS}$; C, 40.16; H, 1.50; N, 5.20. Found: C, 40.36; H, 1.79; N, 4.97.

4-(2-Chloro-4-fluoro-phenylsulfanyl)-azetidin-2-one (9).—66% yield m.p. 84–85°C

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.56 (1H, dd, $J=5.91, 2.70$), 7.30 (1H, dd, $J=2.87, 5.34$), 7.04 (1H, dt, $J=2.71, 5.47$), 6.46 (1H, br, s), 5.02 (1H, dd, $J=2.56, 2.63$), 3.45 (1H, ddd, $J=1.85, 3.08, 8.55$), 2.97 (1H, td, $J=1.83, 11.67$); ^{13}C NMR (125 MHz, CDCl_3): δ 165.65, 164.32, 161.78, 137.58, 126.45, 118.63, 115.09, 54.36, 45.81; IR (neat) $\nu_{\max}$ (C=O) 1756.93 cm^{-1} . *Anal.* calcd for $\text{C}_9\text{H}_7\text{ClFNOS}$; C, 46.66; H, 3.05; Cl, 15.30; F, 8.20; N, 6.05; O, 6.91; S, 13.84. Found: C, 46.97; H, 3.23; Cl, 15.51; F, 8.13; N, 6.22; O, 6.71; S, 13.64.

4-(3-Chloro-4-fluoro-phenylsulfanyl)-azetidin-2-one (10).—56% yield m.p. 97–98°C

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.57 (2H, dd, $J=2.23, 4.61$), 7.39 (1H, ddd, $J=2.23, 2.210, 2.26$), 7.20 (1H, dd, $J=8.61, 3.08$), 6.28 (1H, br, s), 4.99 (1H, dd, $J=2.30, 2.61$), 3.42 (1H, ddd, $J=2.05, 4.52, 12.41$), 2.90 (1H, ddd, $J=1.25, 0.86, 11.87$), 1.64 (1H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 165.54, 159.99, 136.29, 134.31, 130.82, 127.34, 121.99, 117.46, 54.58, 45.47; IR (neat) $\nu_{\max}$ (C=O) 1761.81 cm^{-1} . *Anal.* calcd for $\text{C}_9\text{H}_7\text{ClFNOS}$; C, 46.66; H, 3.05; Cl, 15.30; F, 8.20; N, 6.05; O, 6.91; S, 13.84. Found: C, 46.57; H, 3.28; Cl, 15.41; F, 8.27; N, 6.28; O, 6.86; S, 13.76.

4-(2,4-Dichloro-phenylsulfanyl)-azetidin-2-one (11).—50% yield m.p. 143–144°C

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.53 (1H, d, $J=2.21$), 7.43 (1H, d, $J=8.34$), 7.29 (2H, dt, $J=2.29, 3.35$), 6.32 (1H, br, s), 5.70 (1H, dd, $J=2.32, 2.63$), 3.50 (1H, ddd, $J=1.86, 3.07, 8.50$), 3.02 (1H, td, $J=1.53, 11.56$), 2.20 (3H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 165.32, 138.25, 135.49, 135.20, 130.35, 129.65, 127.97, 99.99, 53.90, 46.02, 30.99; IR (neat) $\nu_{\max}$ (C=O) 1683.76 cm^{-1} ; *Anal.* calcd for $\text{C}_9\text{H}_7\text{Cl}_2\text{NOS}$; C, 43.57; H, 2.84; Cl, 28.57; N, 5.65; O, 6.45; S, 12.92. Found: C, 43.77; H, 2.98; Cl, 28.73; N, 5.57; O, 6.37; S, 12.84.

4-(4-Nitro-phenylsulfanyl)-azetidin-2-one (12).—81% Yield and m.p. 124.03°C

^1H NMR (400 MHz, CDCl_3) δ_{H} 8.19–8.23 (2H, m), 7.46–7.52 (2H, m), 6.24 (1H, br, s), 5.22 (1H, dd, $J=2.24, 2.77$), 3.58 (1H, ddd, $J=1.73, 3.22, 8.69$), 3.05 (1H, ddd, $J=0.79, 1.49$); ^{13}C NMR (125 MHz, CDCl_3) δ 165.95, 130.93, 128.60, 119.92, 119.70, 115.88, 115.67, 54.21, 45.81; IR (neat) $\nu_{\max}$ (C=O) 1700 cm^{-1} ; *Anal.* calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}_3\text{S}$; C, 48.21; H, 3.60; N, 12.49. Found: C, 48.16; H, 3.50; N, 12.39.

4-((2-(trifluoromethyl)phenyl)thio)azetidin-2-one (13).—Purified by recrystallization

in hexane/ethyl acetate to give a yellow-white powder 90% yield with m.p. 81–82 °C. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.75 (1H, d, $J=7.63$), 7.62 (1H, d, $J=7.55$), 7.56 (1H, t, $J=7.11$), 7.47 (1H, t, $J=7.16$), 6.91 (1H, s), 5.03 (1H, dd, $J=2.62, 1.99$), 3.44 (1H, ddd, $J=8.68, 3.10, 1.80$), 2.95 (1H, ddd, $J=14.28, 2.30, 1.02$); ^{13}C NMR (125 MHz, CDCl_3) δ 166.26, 135.88, 132.63, 131.42, 128.80, 127.47, 55.05, 45.99, 31.11; IR (neat) $\nu_{\max}$ (C=O) 1766 cm^{-1} ; *Anal.* calcd for $\text{C}_{10}\text{H}_8\text{F}_3\text{NOS}$; C, 48.58; H, 3.26; N, 5.67. Found: C, 48.73; H, 3.39; N, 5.83.

4-((3-(trifluoromethyl)phenyl)thio)azetidin-2-one (14).—Yield: 83%. m.p. 73-75 °C. ¹H NMR (400 MHz, CDCl₃) δ_H 7.72 (1H, s), 7.67 (1H, d, *J* = 9.15), 7.62 (1H, d, *J* = 9.85), 7.51 (1H, t, *J* = 7.75), 6.80 (1H, s), 5.07 (1H, dd, *J* = 2.62, 2.27), 3.45 (1H, ddd, *J* = 8.52, 3.05, 1.88), 2.92 (1H, ddd, *J* = 14.50, 1.12, 0.80); ¹³C NMR (125 MHz, CDCl₃) δ 166.39, 136.32, 133.41, 131.95 (1C, q, *J* = 0.33), 130.03, 129.75 (1C, q, *J* = 0.03), 125.43 (1C, q, *J* = 0.03), 54.38, 45.83; IR (neat) ν_{max} (C=O) 1766 cm⁻¹; *Anal.* calcd for C₁₀H₈F₃NOS; C, 48.58; H, 3.26; N, 5.67. Found: C, 48.65; H, 3.09; N, 5.63.

4-((4-(trifluoromethyl)phenyl)thio)azetidin-2-one (15).—¹H NMR (400 MHz, CDCl₃) δ_H 7.61 (2H, doublet, *J* = 8.17), 7.51 (2H, doublet, *J* = 8.08), 7.01 (1H, singlet), 5.11 (1H, dd, *J* = 2.65, 2.30), 3.47 (1H, ddd, *J* = 8.45, 3.06, 1.88), 2.95 (1H, ddd, *J* = 11.72, 1.40, 85); ¹³C NMR (125 MHz, CDCl₃) δ 166.43, 137.57, 131.75, 130.13 (1C, q, *J* = 0.33), 126.34, 53.78, 45.91; IR (neat) ν_{max} (C=O) 1764 cm⁻¹; Yield: 81%. m.p. 95-96.5 °C. *Anal.* calcd for C₁₀H₈F₃NOS; C, 48.58; H, 3.26; N, 5.67. Found: C, 48.83; H, 3.29; N, 5.53.

4-((3,5-bis(trifluoromethyl)phenyl)thio)azetidin-2-one (16).—Yield: 79%. m.p. 77-79 °C. ¹H NMR (400 MHz, CDCl₃) δ_H 7.88 (2H, s), 7.86 (1H, s), 6.46 (1H, s), 5.17 (1H, dd, *J* = 2.65, 2.32), 3.55 (1H, ddd, *J* = 8.28, 2.89, 2.11), 3.00 (1H, ddd, *J* = 11.90, 1.26, 0.98); ¹³C NMR (125 MHz, CDCl₃) δ 166.04, 135.93, 132.77 (1C, q, *J* = 0.33), 132.11, 124.30, 122.11, 121.59, 54.22, 46.04; IR (neat) ν_{max} (C=O) 1771 cm⁻¹; *Anal.* calcd for C₁₁H₇F₆NOS; C, 41.91; H, 2.24; N, 4.44. Found: C, 41.83; H, 2.08; N, 4.43.

4-(2-Methoxy-phenylsulfanyl)-azetidin-2-one (17).—Purified by recrystallization in hexane/ethyl acetate to give a white solid 87 % yield with m.p. 106 – 107 °C. ¹H NMR (400 MHz, CDCl₃) δ_H 7.43-6.88 (4H, m), 6.75 (1H, br, s), 4.86 (1H, dd, *J* = 2.23, 2.60), 3.80 (3H, s), 3.28 (1H, ddd, *J* = 1.81, 1.82, 8.53), 2.93 (1H, dq, *J* = 1.36, 1.41, 11.78); ¹³C NMR (125 MHz, CDCl₃) δ 166.56, 160.74, 136.93, 120.82, 114.96, 55.54, 54.90, 44.99; IR (neat) ν_{max} (C=O) 1760 cm⁻¹; *Anal.* calcd for C₁₀H₁₁NO₂S; C, 57.39; H, 5.30; N, 6.69. Found: C, 57.37; H, 5.19; N, 6.67.

4-(3-Methoxy-phenylsulfanyl)-azetidin-2-one (18).—Purification of the crude product (yellow oil with a 75 % yield) was not needed. ¹H NMR (400 MHz, CDCl₃) δ_H 7.29-6.87 (4H, m), 6.07 (1H, brs), 5.03 (1H, dd, *J* = 2.31, 2.64), 3.39 (1H, ddd, *J* = 1.01, 1.27, 9.00), 3.81 (3H, s), 2.91 (1H, dd, *J* = 1.46, 13.75); ¹³C NMR (125 MHz, CDCl₃) δ 169.99, 160.01, 133.17, 130.30, 125.02, 118.24, 114.22, 55.46, 54.22, 45.41; IR (neat) ν_{max} (C=O) 1756 cm⁻¹; *Anal.* calcd for C₁₀H₁₁NO₂S; C, 57.39; H, 5.30; N, 6.69. Found: C, 57.25; H, 5.34; N, 6.52.

4-(4-Methoxy-phenylsulfanyl)-azetidin-2-one (19).—Purified by recrystallization in hexane/ethyl acetate to give a white solid with a 57 % yield and m.p. 83 - 85 °C. ¹H NMR (400 MHz, CDCl₃) δ_H 7.40-6.86 (4H, m), 6.81 (1H, br, s), 4.97 (1H, dd, *J* = 2.30, 2.62), 3.89 (3H, s), 3.37 (1H, ddd, *J* = 1.45, 1.45, 8.82), 2.93 (1H, dt, *J* = 1.89, 11.44); ¹³C NMR (125 MHz, CDCl₃) δ 169.69, 159.16, 134.93, 130.47, 121.44, 111.47, 56.06, 54.06, 45.87; IR (neat) ν_{max} (C=O) 1756 cm⁻¹; *Anal.* calcd for C₁₀H₁₁NO₂S; C, 57.39; H, 5.30; N, 6.69. Found: C, 57.20; H, 5.22; N, 6.58.

4-(2,5-Dimethoxy-phenylsulfanyl)-azetidin-2-one (20).—Purified by recrystallization in hexane/ethyl acetate to give a white solid with a 51 % yield and m.p. 116 - 118°C. ¹H NMR (400 MHz, CDCl₃) δ_H 7.28-6.87 (4H, m), 6.46 (1H, br, s), 5.01 (1H, dd, *J*=2.34, 2.61), 3.78 (3H, s), 3.41 (1H, ddd, *J*=1.40, 1.41, 8.87), 3.86 (3H, s), 2.98 (1H, dt, *J*=2.04, 11.17); ¹³C NMR (125 MHz, CDCl₃) δ 166.26, 153.59, 153.19, 120.93, 120.13, 114.78, 112.22, 56.44, 55.83, 53.88, 45.73; IR (neat) ν_{max} (C=O) 1760 cm⁻¹; *Anal.* calcd for C₁₁H₁₃NO₃S; C, 55.21; H, 5.48; N, 5.85. Found: C, 54.92; H, 5.36; N, 5.81.13

4-(3,4-Dimethoxy-phenylsulfanyl)-azetidin-2-one (21).—Purified by recrystallization in hexane/ethyl acetate to give a white powder with a 63 % yield and m.p. 79 - 80°C. ¹H NMR (400 MHz, CDCl₃) δ_H 7.07-6.34 (4H, m), 6.36 (1H, brs), 4.71 (1H, dd, *J*=2.28, 2.64), 3.68 (3H, s), 3.67 (3H, s), 3.10 (1H, ddd, *J*=1.86, 1.92, 8.38), 2.64 (1H, dq, *J*=1.40, 1.41, 11.60); ¹³C NMR (125 MHz, CDCl₃) δ 171.20, 166.21, 150.12, 149.15, 128.05, 121.20, 117.74, 111.59, 60.41, 56.02, 55.91, 54.78, 44.89, 21.06, 14.19; IR (neat) ν_{max} (C=O) 1760 cm⁻¹; *Anal.* calcd for C₁₁H₁₃NO₃S; C, 55.21; H, 5.48; N, 5.85. Found: C, 55.03; H, 5.40; N, 5.78.

4-(Thiophen-2-ylsulfanyl)-azetidin-2-one (22).—The crude product was crystallized from CH₂Cl₂ and hexanes to afford white crystals (90%) with mp 57–58°C. ¹H NMR (400 MHz, CDCl₃) δ_H 7.48 (1H, dd *J*=1.2, 5.4), 7.23 (1H, dd, *J*=1.2, 3.6), 7.07 (1H, dd, *J*=3.6, 5.4), 6.19 (1H, br, s), 4.86 (1H, dd, *J*=2.3, 4.9), 3.31 (1H, ddd, *J*=1.9, 4.9, 15.3), 2.91 (1H, ddd, *J*=1.6, 2.0, 15.2); ¹³C NMR (125 MHz, CDCl₃) δ 165.52, 136.75, 131.82, 128.12, 127.49, 55.38, 44.72; IR (neat) ν_{max} (C=O) 1739.7.1 cm⁻¹; *Anal.* calcd for C₇H₇NOS₂; C, 45.38; H, 3.81; N, 7.56. Found: C, 45.50; H, 3.76; N, 7.43.

4-(4-Methylsulfanyl-phenylsulfanyl)-azetidin-2-one (23).—White fluffy powder with a 48.7% yield and m.p. 60.16°C

¹H NMR (400 MHz, CDCl₃) δ_H 7.22-7.42 (4H, m), 6.07 (1H, br, s), 4.97 (1H, dd, *J*=2.65, 2.28), 3.36 (1H, ddd, *J*=1.87, 3.06, 8.43), 2.88 (1H, d, *J*=15.22), 2.50 (3H, s); ¹³C NMR (125 MHz, CDCl₃) δ 166.12, 140.67, 134.80, 126.93, 54.63, 45.36, 15.52; IR (neat) ν_{max} (C=O) 1700 cm⁻¹; *Anal.* calcd for C₁₀H₁₁NOS₂; C, 53.30; H, 4.92; N, 6.22. Found: C, 53.33; H, 4.90; N, 6.16.

4-(Naphthalen-1-ylsulfanyl)-azetidin-2-one (24).—73% Yield and m.p. 124.12°C

¹H NMR (400 MHz, CDCl₃): δ_H 8.00 (2H, s), 7.87 (2H, m), 7.55 (3H, m), 7.3 (1H, s), 6.175 (1H, br, s), 5.14 (1H, dd, *J*=2.35, 2.63), 3.45 (1H, ddd, *J*=1.81, 3.11, 8.418), 3.00 (1H, ddd, *J*=1.73, 1.86, 17.04); ¹³C NMR (125 MHz, CDCl₃): δ 165.42, 149.70, 133.63, 132.90, 132.79, 130.16, 129.14, 128.72, 127.81, 126.97, 126.94, 54.29, 45.49; IR (neat) ν_{max} (C=O) 1755cm⁻¹; *Anal.* calcd for C₁₃H₁₁NOS; C, 68.10; H, 4.84; N, 6.11; O, 6.98; S, 13.98. Found: C, 68.35; H, 4.97; N, 6.19; O, 6.79; S, 13.78.

4-(4-Nitro-phenoxy)-azetidin-2-one (25).—Purified by recrystallization in hexane/ethyl acetate to give a beige powder 68% yield with m.p. 124-130°C. ¹H NMR (400 MHz, CDCl₃) δ_H 8.28 (2H, dd, *J*=2.173, 4.89), 6.97 (2H, dd, *J*=2.17, 4.90), 6.56 (1H, br, s), 5.81

(1H, dd, $J=1.21, 2.52$), 3.49 (1H, ddd, $J=1.32, 2.38, 9.05$), 3.2 (1H, ddd, $J=0.5, 0.98, 14.15$); ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{CO}$) δ 166.14, 162.45, 143.17, 126.74, 116.62, 77.40, 46.69; IR (neat) ν_{max} (C=O) 1775 cm^{-1} ; *Anal.* calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.64; H, 4.02; N, 13.46.

4-(4-Trifluoromethyl-phenoxy)-azetidin-2-one (26).—Purified by recrystallization in hexane/ethyl acetate to give a white powder 78% yield with m.p. $95\text{--}98^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.54 (2H, d, $J=8.75$), 6.87 (2H, d, $J=8.69$), 6.53 (1H, br, s), 5.67 (1H, dd, $J=1.09, 2.63$), 3.35 (1H, ddd, $J=1.19, 2.45, 9.00$), 3.07 (1H, d, $J=15.12$); ^{13}C NMR (125 MHz, CDCl_3) δ 166.46, 158.37, 127.36, 125.11, 124.78, 115.43, 76.23, 46.18; IR (neat) ν_{max} (C=O) 1780 cm^{-1} ; *Anal.* calcd for $\text{C}_{10}\text{H}_8\text{F}_3\text{NO}_2$: C, 51.96; H, 3.49; N, 6.06. Found: C, 51.91; H, 3.41; N, 5.97.

4-Phenylselanyl-azetidin-2-one (27).— ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.35–7.89 (5H, m), 6.33 (1H, br, s), 5.14 (1H, dd, $J=2.20, 2.62$), 3.45 (1H, ddd, $J=1.70, 3.15, 8.82$), 2.97 (1H, dt, $J=1.86, 11.64$); ^{13}C NMR (125 MHz, CDCl_3): δ 165.91, 135.79, 129.52, 129.23, 127.76, 47.29, 46.46; IR (neat) ν_{max} (C=O) 1749.95 cm^{-1} ; *Anal.* calcd for $\text{C}_9\text{H}_9\text{NOSe}$: C, 47.80; H, 4.01; N, 6.19; O, 7.07; Se, 34.92. Found: C, 47.92; H, 4.21; N, 6.39; O, 7.27; Se, 34.89.

Lactams **28 (azetidin-2-one)** and **29 (4-Allylsulfanyl-azetidin-2-one)** were purchased from Sigma-Aldrich (**28, 29**).

General Procedure for the Synthesis of N-Carbamoylazetidin-2-one Derivatives (29-36, 40-54, 57, 58, 64, 69 from 2-28 respectively)—The synthetic procedure was adopted from Mulchande et al.⁵ and applied to our compounds.

To a solution of appropriate azetidin-2-one **5** (1.7g, 5.4mmol) in DCM (5 mL) was added to 1.2mol eq. of triethylamine and 1.2 mol eq. of the corresponding isocyanates: benzyl isocyanate, ethyl isocyanate, 2-nitrophenyl isocyanate. The reaction was stirred at room temperature and monitored by TLC. After completion of the reaction, the solution was evaporated under reduced pressure.

General Procedure for the Synthesis of N-Carbamoylazetidin-2-one Derivatives via Irradiation (37-39, 55, 56, 59-63, 65-68, 70)—The synthetic procedure developed in our laboratory using a CEM microwave apparatus was applied to the aforementioned compounds: to a solution of an appropriate azetidin-2-one **5** (0.1g, 0.46mmol) in dichloromethane (4 mL), 2 mol eq. of triethylamine was added followed by addition of 1.1 mol eq. of the corresponding isocyanates: benzyl isocyanate, diphenylmethyl isocyanate, 9H-fluoren-9-yl isocyanate, 1-naphthyl isocyanate, 2-fluorobenzyl isocyanate, 2-fluorophenyl isocyanate, 2-methoxybenzyl isocyanate, diphenylethyl isocyanate, and 1-(1-naphthyl)ethyl isocyanate. The reaction was irradiated under-pressure in the microwave for 10 to 60 minutes at 300W, and 35°C and monitored by TLC and NMR.

2-Oxo-4-phenylsulfanyl-azetidine-1-carboxylic acid benzylamide (30).—73% Yield and m.p. 88.69°C

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.60 (1H, d, $J=6.73$), 7.37 (3H, m), 6.85 (1H, br, s), 5.32 (1H, dd, $J=2.71$, 2.90), 4.53 (1H, dq, $J=5.99$, 7.80, 8.25, 8.97), 3.43 (1H, dd, $J=5.62$, 10.73), 2.85 (1H, dd, $J=2.71$, 13.64); ^{13}C NMR (125 MHz, CDCl_3) δ 165.44, 149.63, 137.82, 135.27, 129.32, 129.30, 128.78, 127.73, 127.69, 127.70, 100.00, 56.69, 43.99, 43.69; IR (neat) ν_{max} (C=O) 1755 cm^{-1} ; *Anal.* calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$; C, 65.36; H, 5.16; N, 8.97; Found: C, 65.58; H, 5.45; N, 8.89;

2-(2-Fluoro-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide

(31).—Purified by flash chromatography from ethyl acetate/hexanes to give 67% yield. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.30-7.61 (4H, m), 7.12-7.18 (5H, m), 6.77 (1H, br, s), 5.35 (1H, dd, $J=2.60$, 2.99), 4.50 (2H, ddd, $J=5.35$, 6.00, 8.50), 3.47 (1H, dd, $J=5.64$, 10.84); 2.94 (1H, dd, $J=2.60$, 13.92); ^{13}C NMR (125 MHz, CDCl_3): δ 164.46, 162.00, 160.39, 149.64, 137.95, 137.77, 132.04, 128.82, 127.63, 116.49, 116.27, 56.29, 43.85, 40.74; IR(neat) ν_{max} (C=O) 1774 , 1709 cm^{-1} ; *Anal.* calcd for $\text{C}_{17}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_2\text{S}$; C, 61.80; H, 4.85; N, 8.45. Found: C, 61.95; H, 4.62; N, 8.45.

2-(3-Fluoro-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide

(32).—Clear yellow oil purified by flash chromatography from ethyl acetate/hexanes to give 70% yield. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.07-7.40 (9H, m), 6.84 (1H, br, s), 5.33 (1H, dd, $J=2.75$, 2.90), 4.52 (2H, ddd, $J=5.93$, 6.04, 6.12), 3.46 (1H, dd, $J=5.70$, 10.70), 2.94 (1H, dd, $J=2.75$, 13.66); ^{13}C NMR (125 MHz, CDCl_3) δ 165.44, 149.77, 138.04, 132.60, 130.70, 130.13, 128.95, 127.84, 121.35, 121.13, 116.39, 116.18, 56.98, 44.47, 43.82; IR (neat) ν_{max} (C=O) 1774 , 1709 cm^{-1} ; *Anal.* calcd for $\text{C}_{17}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_2\text{S}$; C, 61.80; H, 4.58; N, 8.44. Found: C, 61.77; H, 4.49; N, 8.44.

2-(4-Fluoro-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide

(33).—Purified by flash chromatography from ethyl acetate/hexanes to give 60% yield. and m.p. 89.71°C ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.01-7.58 (9H, m), 6.84 (1H, br, s), 5.26 (1H, dd, $J=2.91$, 2.73), 4.52 (2H, ddd, $J=11.34$, 8.81, 6.05), 3.44 (1H, dd, $J=10.73$, 5.66); 2.89 (1H, dd, $J=2.74$, 13.65); ^{13}C NMR (125 MHz, CDCl_3) δ 165.44, 165.01, 162.52, 149.79, 137.83, 128.96, 127.88, 124.72, 116.77, 116.56, 57.22, 44.07; IR (neat) ν_{max} (C=O) 1774 , 1709 cm^{-1} ; *Anal.* calcd for $\text{C}_{17}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_2\text{S}$; C, 61.80; H, 4.58; N, 8.44. Found: C, 61.75; H, 4.49; N, 8.47.

2-(2,4-Difluoro-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide

(34).—Purified by ethyl acetate/hexane wash ($5 \times 20\text{ml}$) to give 97.4% yield with m.p.

134-136°C. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.44 (1H, dd J = 6.51, 1.80), 7.14-7.25 (3H, m), 6.69-6.80 (3H, m), 5.15 (1H, q J = 2.73), (1H, ddd J = 6.02, 8.88, 12.04), 3.32 (1H, dd J = 5.69, 10.79); 2.79 (1H, dd J = 2.64, 13.84); ^{13}C NMR (125 MHz, CDCl_3) δ 165.24, 163.12, 162.51, 149.64, 139.30, 137.96, 128.84, 127.74, 112.53, 105.05, 56.59, 44.23, 43.84; IR (neat) ν_{max} (C=O) 1774, 1709 cm^{-1} ; *Anal.* calcd for $\text{C}_{17}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_2\text{S}$; C, 58.61; H, 4.05; N, 8.04. Found: C, 58.53; H, 4.06; N, 8.03.

N-benzyl-2-((3,4-difluorophenyl)thio)-4-oxoazetidine-1-carboxamide (35).—

Purified by ethyl acetate/hexane wash to give 97.4% yield and m.p. 89.24°C. ^1H NMR (400 MHz, CDCl_3) δ_{H} 6.90-7.49 (8H, m), 6.75 (1H, brs), 5.17 (1H, d, J = 2.70, 2.96), 4.43 (2H, ddd J = 5.93, 9.04, 11.40), 3.35 (1H, dd, J = 5.69, 10.69); 2.80 (1H, dd, J = 2.69, 13.70); ^{13}C NMR (125 MHz, CDCl_3): δ 165.28, 164.85, 162.36, 149.60, 137.76, 128.80, 127.74, 124.47, 116.55, 57.06, 43.70; IR (neat) ν_{max} (C=O) 1775, 1700 cm^{-1} ; *Anal.* calcd for $\text{C}_{17}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_2\text{S}$; C, 58.61; H, 4.05; N, 8.04. Found: C, 61.77; H, 4.49; N, 8.44.

N-benzyl-2-oxo-4-((perfluorophenyl)thio)azetidine-1-carboxamide (36).—

Cloudy yellow oil Purified by preparatory plate on silica gel (3:1 Hexanes: Ethyl acetate) to give 37.5% yield. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.39-7.26 (3H, m), 6.69 (1H, br, s), 5.46 aH, dd J = 2.89, 2.96), 4.5 (1H, dq, J = 9.09, 5.84), 3.60 (dd J = 5.85, J = 10.62, 1H), 2.99 (dd J = 2.85, J = 13.625, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.11, 149.21, 128.78, 127.58, 77.36, 55.66, 43.76; IR (neat) ν_{max} (C=O) 1775, 1700 cm^{-1} . *Anal.* calcd for $\text{C}_{17}\text{H}_{11}\text{F}_5\text{N}_2\text{O}_2\text{S}$; C, 50.75; H, 2.76; N, 6.96. Found: C, 50.96; H, 2.93; N, 6.61.

2-(2-Chloro-4-fluoro-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide (37).—

Yield 43.3% m.p. 116-119°C

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.72 (1H, dd, J = 6.00, 2.65), 7.35 (2H, m), 6.97 (1H, dt, J = 2.82, 5.13), 5.36 (1H, dd, J = 2.77, 2.94), 6.82 (1H, br, s), 4.48 (1H, dq, J = 6.01, 8.56), 3.51 (1H, dd, J = 5.73, 11.77), 2.98 (1H, dd, J = 2.78, 13.69), 2.20 (1H, s); 1.65 (1H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 165.14, 149.51, 138.62, 137.69, 128.78, 127.71, 117.92, 114.98, 56.91, 44.01, 44.73; IR (neat) ν_{max} (C=O) 1772.41, 1700.35 cm^{-1} . *Anal.* calcd for $\text{C}_{17}\text{H}_{14}\text{ClFN}_2\text{O}_2\text{S}$; C, 55.97; H, 3.87; Cl, 9.72; F, 5.21; N, 7.68; O, 8.77; S, 8.79. Found: C, 56.17; H, 4.07; Cl, 9.81; F, 5.19; N, 7.83; O, 8.68; S, 8.67.

2-(3-Chloro-4-fluoro-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide (38).—

Yield 37.8%-oil

¹H NMR (400 MHz, CDCl₃) δ_H 7.70 (1H, dd, *J*=2.24, 4.64), 7.50 (1H, ddd, *J*=3.27, 2.12, 1.75), 7.36 (3H, m), 7.12 (1H, t, *J*=8.64), 6.85 (1H, br, s), 5.28 (1H, dd, *J*=2.78, 2.92), 4.52 (2H, q, *J*=6.07), 3.50 (1H, dd, *J*=5.72, 10.70), 2.93 (1H, dd, *J*=2.78, 13.63); 2.20 (3H, s); ¹³C NMR (125 MHz, CDCl₃) δ 165.06, 160.14, 149.54, 137.65, 137.14, 135.20, 128.82, 127.73, 126.51, 121.85, 121.66, 117.42, 57.32, 44.19, 43.74, 30.98; IR (neat) ν_{max} (C=O) 1774.60, 1704.76 cm⁻¹. *Anal.* calcd for C₁₇H₁₄ClFN₂O₂S: C, 55.97; H, 3.87; Cl, 9.72; F, 5.21; N, 7.68; O, 8.77; S, 8.79. Found: C, 56.08; H, 3.80; Cl, 9.51; F, 5.17; N, 7.61; O, 8.73; S, 8.57.

2-(2,4-Dichloro-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide (39).—Yield 28.2% m.p. 95-97°C

¹H NMR (400 MHz, CDCl₃) δ_H 7.58 (1H, d, *J*=8.40), 7.40 (1H, d, *J*=2.22), 7.25 (2H, m), 7.13 (1H, dd, *J*=2.23, 6.16), 6.73 (1H, br, s), 5.29 (1H, dd, *J*=2.81, 2.90), 4.39 (2H, q, *J*=6.07), 3.44 (1H, dd, *J*=5.74, 10.72), 2.91 (1H, dd, *J*=2.80, 13.66), 2.10 (1H, s); ¹³C NMR (125 MHz, CDCl₃) δ 165.08, 149.50, 138.63, 137.65, 136.75, 135.77, 130.03, 128.91, 128.79, 127.86, 127.72, 56.62, 44.25, 43.74; IR(neat) ν_{max} (C=O) 1774.53, 1705.07 cm⁻¹. *Anal.* calcd for C₁₇H₁₄Cl₂N₂O₂S: C, 53.55; H, 3.70; Cl, 18.60; N, 7.35; O, 8.39; S, 8.41. Found: C, 53.78; H, 3.82; Cl, 18.57; N, 7.48; O, 8.31; S, 8.39.

N-benzyl-2-((4-nitrophenyl)thio)-4-oxoazetidine-1-carboxamide (40).—76% Yield and m.p. 123.04°C

¹H NMR (400 MHz, CDCl₃) δ_H 7.29-7.56 (10H, m), 6.82 (1H, br, s), 6.78 (1H, dd *J*=2.72, 2.88), 5.42 (1H, dd, *J*=2.78, 2.95), 4.42 (2H, d, *J*=5.57), 3.59 (1H, dd *J*=5.76, 10.56), 3.0 (1H, dd *J*=2.93, 13.62); ¹³C NMR (125 MHz, CDCl₃) δ 164.94, 149.69, 147.22, 141.97, 137.61, 131.59, 129.00, 127.98, 127.84, 124.25, 56.80, 45.12, 43.98; IR (neat) ν_{max} (C=O) 1775, 1700 cm⁻¹; *Anal.* calcd for C₁₇H₁₅N₃O₄S: C, 57.13; H, 4.23; N, 11.76. Found: C, 57.43; H, 4.37; N, 12.01.

N-benzyl-2-oxo-4-((2-(trifluoromethyl)phenyl)thio)azetidine-1-carboxamide (41).—MP: Viscous Oil (N/A). Yield: 66%.

¹H NMR (400 MHz, CDCl₃) δ_H 7.84 (1H, d, *J*= 7.49), 7.67 (1H, d, *J*= 7.65), 7.19-7.31 (1H, m); 7.39-7.48 (2H, m), 6.76 (1H, s), 5.28 (1H, dd, *J*= 2.92, 2.78), 4.33 - 4.47 (1H, m), 3.42 (1H, dd, *J*= 10.80, 5.75), 2.87 (1H, dd, *J*= 13.74, 2.83); ¹³C NMR (125 MHz, CDCl₃) δ 165.49, 149.77, 137.92, 137.69, 134.46 (1C, q, *J*= 0.3), 132.54, 130.49, 129.23, 128.95, 127.86, 127.81, 127.22 (1C, q, *J*= 0.05), 58.18, 44.62, 43.87; IR (neat) ν_{max} (C=O) 1778, 1706 cm⁻¹; *Anal.* calcd for C₁₈H₁₅F₃N₂O₂S: C, 56.84; H, 3.97; N, 7.36; Found: C, 56.92; H, 4.03; N, 7.45.

RK4 N-benzyl-2-oxo-4-((3-(trifluoromethyl)phenyl)thio)azetidine-1-carboxamide (42).—MP: Viscous Oil (N/A). Yield: 67.5%

¹H NMR (400 MHz, CDCl₃) δ_H 7.77 (1H, singlet), 7.74 (1H, d, *J*= 7.85), 7.54 (1H, d, *J*= 7.80), 7.39 (1H, t, *J*= 7.81), 7.18-7.29(2H, m), 6.72 (1H, br, s), 5.26 (1H, dd, *J*= 2.77, 1.55), 4.41 (1H, d, *J*= 5.95), 3.41 (1H, dd, *J*= 10.72, 5.92), 2.82 (1H, dd, *J*= 13.66, 2.77); ¹³C NMR (125 MHz, CDCl₃) δ 165.20, 149.71, 137.79, 137.74, 132.13, 44.57, 131.74 (1C, q, *J*

= 0.32), 131.14, 129.88, 128.95, 127.88, 127.85, 125.90, 57.21, 43.91; IR (neat) $\nu_{\max}$ (C=O) 1777, 1706 cm^{-1} ; *Anal.* calcd for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_2\text{S}$; C, 56.84; H, 3.97; N, 7.36; Found: C, 57.01; H, 4.02; N, 7.46;

RK6 N-benzyl-2-oxo-4-((4-(trifluoromethyl)phenyl)thio)azetidine-1-carboxamide (43).—MP: 72-73 °C. Yield: 64%.

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.67 (1H, dd, J = 43.02, 8.11), 7.29-7.41 (2H, m), 6.87 (1H, br, s), 5.41 (1H, dd, J = 2.93, 2.81), 4.52 (1H, d, J = 5.99), 3.57 (1H, dd, J = 10.71, 5.74), 2.99 (1H, dd, J = 13.63, 2.81); ^{13}C NMR (125 MHz, CDCl_3) δ 165.26, 149.75, 137.81, 136.34, 133.38, 30.62 (1C, q, J = 0.33), 127.87, 126.20, 57.01, 44.86, 127.93, 128.98, 143.91; IR (neat) $\nu_{\max}$ (C=O) 1778, 1708 cm^{-1} ; *Anal.* calcd for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_2\text{S}$; C, 56.84; H, 3.97; N, 7.36; Found: C, 56.98; H, 4.01; N, 7.39.

N-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)thio)-4-oxoazetidine-1-carboxamide (44).—MP: 61-62 °C. Yield: 65%.

^1H NMR (400 MHz, CDCl_3) δ_{H} 8.05 (1H, s), 7.77 (1H, s), 7.19 - 7.30 (3H, m), 6.72 (1H, s), 5.33 (1H, dd, J = 2.94, 2.89), 4.36-4.46 (2H, m), 3.53 (1H, dd, J = 10.64, 5.82), 2.91 (1H, dd, J = 13.62, 2.89); ^{13}C NMR (125 MHz, CDCl_3) δ 164.80, 149.62, 137.61, 135.40, 133.26, 132.52 (2C, q, J = 0.33), 128.97, 127.94, 127.88, 124.40, 122.45, 121.68, 57.49, 44.83, 43.99; IR (neat) $\nu_{\max}$ (C=O) 1780, 1707 cm^{-1} ; *Anal.* calcd for $\text{C}_{19}\text{H}_{14}\text{F}_6\text{N}_2\text{O}_2\text{S}$; C, 50.89; H, 3.15; N, 6.25; Found: C, 50.93; H, 3.42; N, 6.41;

N-benzyl-2-((2-methoxyphenyl)thio)-4-oxoazetidine-1-carboxamide (45).—

Purified by recrystallization in hexane/ethyl acetate to give a white powder with a 90% yield and m.p. 105 - 107 °C. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.55-6.81 (4H, m), 5.38 (1H, dd, J = 2.62, 2.96), 3.40 (1H, dd, J = 5.62, 10.71), 3.86 (3H, s), 2.94 (1H, dd, J = 2.62, 13.75); ^{13}C NMR (125 MHz, CDCl_3) δ 165.70, 159.93, 149.61, 137.88, 137.28, 131.25, 128.74, 127.75, 127.64, 121.25, 117.37, 111.22, 55.81, 43.94, 43.65; IR (neat) $\nu_{\max}$ (C=O) 1627, 1576 cm^{-1} ; *Anal.* calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$; C, 63.14; H, 5.30; N, 8.18. Found: C, 63.40; H, 5.28; N, 8.32.

N-benzyl-2-((3-methoxyphenyl)thio)-4-oxoazetidine-1-carboxamide (46).—

Purified via a flash column chromatography with a ratio gradient of 3:1 hexane and dichloromethane to produce a colorless oil with a 57 % yield. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.25-6.74 (4H, m), 5.19 (1H, dd, J = 2.70, 2.93), 3.22 (1H, dd, J = 1.84, 3.09), 3.68 (3H, s), 2.78 (1H, dt, J = 1.32, 13.74); ^{13}C NMR (125 MHz, CDCl_3) δ 165.53, 159.87, 149.63, 137.79, 130.47, 130.04, 128.78, 127.74, 127.13, 120.01, 115.34, 56.60, 55.35, 44.01, 43.69; IR (neat) $\nu_{\max}$ (C=O) 1775, 1700 cm^{-1} ; *Anal.* calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$; C, 63.14; H, 5.30; N, 8.18. Found: C, 63.57; H, 5.51; N, 8.05.

N-benzyl-2-((4-methoxyphenyl)thio)-4-oxoazetidine-1-carboxamide (47).—

Purified by recrystallization in hexane/ethyl acetate to give a white powder with a 58% yield and a m.p. 105 - 110 °C. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.48-6.84 (4H, m), 5.21 (1H, dd, J = 2.65, 2.91), 3.82 (3H, s), 3.36 (1H, dd, J = 5.61, 10.69), 2.86 (1H, dd, J = 2.67, 13.65); ^{13}C

NMR (125 MHz, CDCl₃) δ 194.66, 165.53, 160.88, 137.95, 128.76, 127.78, 127.67, 118.74, 114.83, 56.72, 55.35, 43.64, 43.39; IR (neat) $\nu_{\max}$ (C=O) 1775, 1700 cm⁻¹; *Anal.* calcd for C₁₈H₁₈N₂O₃S; C, 63.14; H, 5.30; N, 8.18. Found: C, 63.34; H, 5.13; N, 8.18.

N-benzyl-2-((2,5-dimethoxyphenyl)thio)-4-oxoazetidine-1-carboxamide (48).—A

white solid with a 88 % yield and a m.p. 87.5 – 88.5°C. ¹H NMR (400 MHz, CDCl₃) δ_{H} 7.48–6.84 (4H, m), 5.21 (1H, dd, *J*=2.65, 2.91), 3.82 (3H, s), 3.36 (1H, dd, *J*=5.61, 10.69), 2.86 (1H, dd, *J*=2.67, 13.65); ¹³C NMR (125 MHz, CDCl₃) δ 128.75, 128.63, 127.74, 127.64, 127.49, 121.90, 116.30, 112.16, 56.35, 44.04, 43.67; IR (neat) $\nu_{\max}$ (C=O) 1775, 1705 cm⁻¹; *Anal.* calcd for C₁₉H₂₀N₂O₄S; C, 61.27; H, 5.41; N, 7.52. Found: C, 61.04; H, 5.39; N, 7.47.

N-benzyl-2-((3,4-dimethoxyphenyl)thio)-4-oxoazetidine-1-carboxamide (49).—

Clear oil with a 63 % yield. ¹H NMR (400 MHz, CDCl₃) δ_{H} 7.48–6.84 (4H, m), 5.21 (1H, dd, *J*=2.65, 2.91), 3.82 (3H, s), 3.36 (1H, dd, *J*=5.61, 10.69), 2.86 (1H, dd, *J*=2.67, 13.65); ¹³C NMR (125 MHz, CDCl₃) δ 165.59, 150.38, 149.68, 149.03, 137.93, 129.29, 128.73, 127.75, 127.64, 119.13, 118.98, 111.37, 56.74, 55.88, 43.58, 43.37; IR (neat) $\nu_{\max}$ (C=O) 1775, 1705 cm⁻¹; *Anal.* calcd for C₁₉H₂₀N₂O₄S; C, 61.27; H, 5.41; N, 7.52. Found: C, 61.54; H, 5.56; N, 7.43.

N-benzyl-2-oxo-4-(thiophen-3-ylthio)azetidine-1-carboxamide (50).—72% Yield and oil product

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.25 (4H, m), 7.12 (1H, dd, *J*=0.85, 2.37), 6.95 (1H, dd, *J*=1.736, 3.58), 6.68 (1H, br, s), 5.05 (1H, dd, *J*=2.58, 2.91), 4.42 (1H, dq, *J*=4.49, 6.10, 8.97), 3.25 (1H, dd, *J*=5.5, 10.82), 2.85 (dd, *J*=2.57, *J*=13.78, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 165.23, 149.48, 138.16, 137.78, 128.15, 128.75, 127.77, 127.69, 125.34, 56.49, 43.71, 43.11, 30.98, 29.73; IR (neat) $\nu_{\max}$ (C=O) 1770, 1700 cm⁻¹; *Anal.* calcd for C₁₅H₁₄N₂O₂S₂; C, 56.58; H, 4.43; N, 8.80. Found: C, 56.72; H, 4.65; N, 8.92.

N-benzyl-2-((4-(methylthio)phenyl)thio)-4-oxoazetidine-1-carboxamide (51).—

Clear oil with a 66.1% yield.

¹H NMR (400 MHz, CDCl₃) δ_{H} 7.16–7.47 (9H, m), 6.84 (1H, br, s), 5.26 (1H, dd, *J*=2.69, 2.92), 4.53 (2H, ddd, *J*=5.57, 8.94, 12.69), 3.42 (1H, dd, *J*=10.75, 5.62), 2.89 (1H, dd, *J*=2.70, 13.64), 2.49 (3H, s); ¹³C NMR (125 MHz, CDCl₃) δ 165.43, 149.65, 141.11, 137.99, 135.93, 128.77, 127.67, 124.67, 56.76, 43.79, 43.64, 15.20; IR (neat) $\nu_{\max}$ (C=O) 1700, 1780 cm⁻¹; *Anal.* calcd for C₁₈H₁₈N₂O₂S; C, 60.31; H, 5.06; N, 7.81. Found: C, 60.50; H, 5.05; N, 7.89.

N-benzyl-2-(naphthalen-1-ylthio)-4-oxoazetidine-1-carboxamide (52).—Opaque oil yield 73%

¹H NMR (400 MHz, CDCl₃) δ_{H} 8.1 (1H, s), 7.65 (4H, m), 6.87 (1H, br, s), 5.40 (1H, dd, *J*=2.57, 2.93), 4.56 (2H, dq, *J*=6.02, 6.09, 8.78, 18.47), 3.42 (1H, dd, *J*=5.64, 10.694), 2.95 (1H, dd, *J*=2.65, 13.69); ¹³C NMR (125 MHz, CDCl₃): δ 165.42, 149.70, 135.11, 137.92,

133.54, 133.20, 131.55, 128.96, 128.82, 127.86, 127.81, 127.78, 127.71, 127.16, 126.80, 126.63, 56.72, 44.09, 43.71, 29.76; IR (neat) $\nu_{\max}$ (C=O) 1780, 1700 cm^{-1} ; *Anal.* calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$; C, 69.59; H, 5.01; N, 7.73; Found: C, 69.79; H, 5.30; N, 7.55.

N-benzyl-2-(4-nitrophenoxy)-4-oxoazetidine-1-carboxamide (53).—Purified by recrystallization in hexane/ethyl acetate to give yellow crystals 72% yield with m.p. 123–124°C. ^1H NMR (400 MHz, CDCl_3) δ_{H} 8.28 (2H, d, $J=9.18$); 7.28–7.41 (7H, m), 6.86 (1H, br, s), 6.18 (1H, dd, $J=1.47, 2.75$), 4.51 (2H, p, $J=5.99, 6.32, 9.10$), 3.58 (1H, dd, $J=4.26, 11.93$), 3.25 (1H, d, $J=16.20$); ^{13}C NMR (125 MHz, CDCl_3) δ 164.73, 161.08, 149.38, 143.04, 137.31, 128.84, 127.84, 127.69, 125.89, 116.65, 78.12, 45.54, 43.84; IR (neat) $\nu_{\max}$ (C=O) 1715, 1775 cm^{-1} ; *Anal.* calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_5$; C, 59.82; H, 4.43; N, 12.31. Found: C, 59.67; H, 4.53; N, 12.20.

N-benzyl-2-oxo-4-(4-(trifluoromethyl)phenoxy)azetidine-1-carboxamide (54).—Purified by recrystallization in hexane/ethyl acetate to give a white powder 70% yield with m.p. 103–109°C. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.54 (2H, d, $J=8.55$), 7.17–7.31 (7H, m), 6.79 (1H, br, s), 6.04 (1H, dd, $J=1.57, 2.68$), 4.43 (2H, p, $J=5.87, 6.05, 8.99$), 3.44 (1H, dd, $J=4.265, 11.85$), 3.11 (1H, dd, $J=1.60, 14.52$); ^{13}C NMR (125 MHz, CDCl_3) δ 165.05, 158.68, 149.47, 137.42, 128.82, 127.78, 127.69, 127.19, 127.08, 125.34, 122.78, 116.76, 78.27, 45.52, 43.80; IR (neat) $\nu_{\max}$ (C=O) 1690, 1780 cm^{-1} ; *Anal.* calcd for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_3$; C, 59.34; H, 4.15; N, 7.69. Found: C, 59.31; H, 4.37; N, 7.63.

N-benzyl-2-oxo-4-(phenylselanyl)azetidine-1-carboxamide (55).—Yield 30.5% ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.66 (1H, d, $J=7.70$), 7.57 (2H, m), 6.83 (1H, br, s), 5.38 (1H, dd, $J=2.58, 2.96$), 3.45 (1H, dd, $J=5.59, 10.89$), 2.90 (1H, dd, $J=2.57, 13.92$); ^{13}C NMR (125 MHz, CDCl_3) δ 165.49, 149.60, 137.84, 136.83, 129.35, 128.78, 127.72, 127.32, 126.32, 125.05, 48.15, 44.66, 43.69, 14.24; IR (neat) $\nu_{\max}$ (C=O) 1771.21, 1701.02 cm^{-1} ; *Anal.* calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2\text{Se}$; C, 56.83; H, 4.49; N, 7.80; O, 8.91; Se, 21.98. Found: C, 56.97; H, 4.69; N, 7.73; O, 8.74; Se, 22.07.

N-benzyl-2-oxoazetidine-1-carboxamide (56).—The synthesis was performed as developed in our laboratory: to a solution of appropriate azetidin-2-one **5** (0.1g, 0.46mmol) in dichloromethane (4 mL), was added 1.2 mol eq. of triethylamine and 1.1 mol eq. of the corresponding isocyanate: 2-fluorobenzyl isocyanate, 2-fluorophenyl isocyanate, and 2-methoxybenzyl isocyanate. The reaction was irradiated under pressure in CEM microwave for 10 to 60 minutes at 300W, and 35°C and monitored by TLC and NMR.

After 10 minutes of irradiation as described above, the product was confirmed by NMR, but once the solvent was evaporated, the product proved unstable within 24 hours. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.13–7.28 (1H, m), 4.39 (1H, d, $J=6.02$), 3.55 (1H, t, $J=4.76$), 2.95 (1H, t, $J=4.77$), 1.187 (1H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 167.05, 150.62, 137.94, 128.50, 128.21, 43.68, 37.23, 36.07, 30.07; IR(neat) $\nu_{\max}$ (C=O) 1760, 1700 cm^{-1} .

2-(allylthio)-N-benzyl-4-oxoazetidine-1-carboxamide (57).—Yield 33%

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.27-7.36 (9H, m), 6.90 (1H, br, s), 5.88 (1H, m), 5.33 (2H, d, $J=16.01$), 5.19 (1H, d, $J=9.99$), 4.50 (2H, s), 3.92 (1H, dd, $J=4.01$, 9.04), 3.42 (2H, ddd, $J=10.12$, 5.36, 2.02), 2.92 (1H, d, $J=16.30$); Unstable, it appears to undergo a [2+2] cycloreversion.

1-Hex-5-ynoyl-4-phenylsulfanyl-azetidin-2-one (58).—Yellow oil with a 10.2% yield.

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.36-7.56 (6H, m), 5.25 (2H, dd, $J=2.96$, 3.18), 3.43 (2H, dd, $J=6.154$, 10.55), 2.93 (2H, dd, $J=13.54$, 3.17), 2.85 (2H, dt, $J=4.43$, 2.83), 2.60 (1H, t, $J=7.25$), 2.54 (2H, t, $J=7.39$), 2.19-2.34 (1H, m), 2.25 (1H, dt, $J=2.58$, 4.20), 2.01 (2H, t, $J=2.67$), 1.92 (2H, dt, $J=1.65$, 5.50); ^{13}C NMR (125 MHz, CDCl_3) δ 169.78, 163.40, 135.19, 129.40, 127.30, 83.18, 69.34, 55.60, 43.76, 35.29, 31.00, 23.30, 22.49, 22.20, 17.77; IR (neat) ν_{max} (C=O) 1700, 1795 cm^{-1} ; Unstable, very prone to hydrolysis.

2-Oxo-4-phenylsulfanyl-azetidine-1-carboxylic acid benzhydryl-amide (59).—To a solution of **2** (0.107 g, 0.596 mmol) and diphenylmethyl isocyanate (0.116 mL, 0.615 mmol) in methylene chloride (5 mL) was added triethylamine (85.5 μL , 0.614 mmol). The solution was microwave irradiated under pressure at 70° C for 20 minutes. The solution was washed with 5% HCl (10 mL aliquots) and the resulting organics were purified by column chromatography with a linear mobile phase gradient (10:1 methylene chloride/ethyl acetate to 1:10 methylene chloride/ethyl acetate) which gave the product **7** (0.19 g, 86.3%) as a light brown gel. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.54 (4H, d, $J=7.78$), 7.31 (10H, m), 7.21 (1H, s), 5.99 (1H, br, s), 5.29 (1H, dd, $J=2.86$, 2.74), 3.44 (1H, dd, $J=10.77$, 5.67), 2.91 (1H, dd, $J=13.66$, 2.74).

2-Oxo-4-phenylsulfanyl-azetidine-1-carboxylic acid (9H-fluoren-9-yl)-amide (60).—To a solution of **2** (0.119 g, 0.664 mmol) and 9H-fluoren-9-yl isocyanate (0.141 g, 0.798 mmol) in methylene chloride (5 mL) was added triethylamine (95.3 μL , 0.683 mmol). The solution was microwave irradiated under pressure at 70° C for 15 minutes. The solution was washed with 5% HCl (10 mL aliquots) and the resulting organics were purified by column chromatography with a linear mobile phase gradient (10:1 methylene chloride/ethyl acetate to 1:10 methylene chloride/ethyl acetate) which gave the product **7** (0.22 g, 89.7%) as a yellow crystal. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.50 (2H, m), 7.45 (2H, m), 7.18 (8H, m), 6.55 (1H, d, $J=8.78$), 5.95 (2H, d, $J=8.79$), 5.18 (1H, dd, $J=2.93$, 2.73), 3.19 (1H, dd, $J=10.74$, 5.67), 2.67 (1H, dd, $J=13.66$, 2.75); ^{13}C NMR (125 MHz, CDCl_3) δ 148.16,

141.66, 141.36, 138.31, 133.07, 127.14, 127.05, 126.69, 125.63, 122.86, 117.89, 54.56, 52.55, 41.81. *Anal.* calcd for $C_{23}H_{18}N_2O_2S$: C, 71.48; H, 4.69; N, 7.25; O, 8.28; S, 8.30. Found: C, 71.64; H, 4.68; N, 7.43; O, 8.47; S, 8.51.

2-Oxo-4-phenylsulfanyl-azetidine-1-carboxylic acid naphthalen-1-ylamide (61).

—To a solution of **2** (0.139 g, 0.775 mmol) and 1-naphthyl isocyanate (0.115 mL, 0.679 mmol) in methylene chloride (5 mL) was added triethylamine (0.111 mL, 1.09 mmol). The solution was irradiated using CEM microwave at 70° C for 20 minutes. The solution was then washed with 5% HCl (10 mL aliquots) and resulting organic layer was evaporated and purified by column chromatography with a linear mobile phase gradient (10:1 methylene chloride/ethyl acetate to 1:10 methylene chloride/ethyl acetate) affording **6** (0.21 g, 82.5%) as a clear, colorless gel. 1H NMR (400 MHz, $CDCl_3$) δ_H 9.09 (1H, s), 8.21 (1H, d, $J=7.01$), 7.93 (1H, dd, $J=9.22, 8.39$), 7.66 (1H, m); 7.72 (1H, d, $J=8.25$), 7.56 (2H, m), 7.42 (4H, m), 7.40 (1H, s), 5.54 (1H, dd, $J=2.91, 2.76$), 3.56 (1H, dd, $J=10.73, 5.68$), 3.05 (1H, dd, $J=13.65, 2.74$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.30, 147.45, 135.33, 134.01, 131.69, 129.44, 129.34, 128.83, 126.66, 126.18, 125.86, 125.73, 125.20, 120.14, 118.59, 57.24, 44.15. *Anal.* calcd for $C_{20}H_{16}N_2O_2S$: C, 68.95; H, 4.63; N, 8.04; O, 9.18; S, 9.20. Found: C, 69.07; H, 4.78; N, 7.94; O, 9.11; S, 9.12.

N-benzhydryl-2-((4-fluorophenyl)thio)-4-oxoazetidine-1-carboxamide (62).—

Yield 28.7% - waxy solid

1H NMR (400 MHz, $CDCl_3$) δ_H 7.52 (1H, dd, $J=3.16, 2.78$), 7.34 (2H, m), 7.00 (1H, t, $J=8.60$), 6.27 (1H, d, $J=8.69$), 5.25 (1H, dd, $J=2.71, 2.91$), 4.15 (1H, q, $J=7.12$), 3.46 (1H, dd, $J=5.65, 10.75$), 2.91 (1H, dd, $J=2.72, 13.69$), 2.08 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.48, 164.87, 162.38, 148.82, 141.31, 140.93, 137.91, 128.80, 127.76, 127.28, 124.20, 116.48, 60.44, 57.15, 43.99, 29.75; IR (neat) ν_{max} (C=O) 1770.42, 1708.96 cm^{-1} . *Anal.* calcd for $C_{23}H_{19}FN_2O_2S$: C, 67.96; H, 4.71; F, 4.67; N, 6.89; O, 7.87; S, Found: C, 68.16; H, 4.81; F, 4.65; N, 6.95; O, 7.73; S, 7.79.

N-(2,2-diphenylethyl)-2-((4-fluorophenyl)thio)-4-oxoazetidine-1-carboxamide (63).—Yield 32% MP 155-156°C

1H NMR (400 MHz, $CDCl_3$) δ_H 7.34 (1H, dd, $J=1.25, 2.67$), 7.23 (2H, m), 6.87 (1H, t, $J=3.80$), 6.41 (1H, br, s), 5.09 (1H, dd, $J=2.72, 2.89$), 4.22 (1H, t, $J=7.99$), 4.02 (1H, dd, $J=5.98, 1.89$), 3.97 (1H, dd, $J=5.95, 1.82$), 3.80 (1H, dd, $J=5.52, 2.30$), 3.76 (1H, dd, $J=5.57, 2.32$), 3.23 (1H, dd, $J=5.66, 10.66$), 2.63 (1H, dd, $J=2.71, 13.61$), 2.10 (3H, s), 1.52 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.00, 141.54, 141.41, 137.85, 128.80, 128.08, 126.99, 124.11, 116.59, 116.37, 56.61, 50.87, 44.07, 43.45; IR (neat) ν_{max} (C=O) 1772.23, 1705.13 cm^{-1} . *Anal.* calcd for $C_{24}H_{21}FN_2O_2S$: C, 68.55; H, 5.03; F, 4.52; N, 6.66; O, 7.61; S, 7.62. Found: C, 68.72; H, 5.24; F, 4.63; N, 6.67; O, 7.52; S, 7.83.

2-((2,4-Difluorophenyl)Thio)-N-Ethyl-4-Oxoazetidine-1-Carboxamide (64).—

Purified by flash chromatography on silica gel with 2:1 Hexanes: Ethyl acetate to give 95% yield. 1H NMR (400 MHz, $CDCl_3$) δ_H 7.63 (1H, q, $J=8.11, 6.79$), 7.25 (1H, s), 6.92 (1H, t, $J=8.09$), 6.39 (1H, br, s), 5.26 (1H, dd $J=2.96, 2.70$), 3.462 (1H, dd, $J=10.75, 5.66$), 3.33

(1H, p, $J=7.07, 6.27$), 2.90 (1H, dd, $J=13.68, 2.72$), 1.20 (1H, d, $J=7.24$); ^{13}C NMR (125 MHz, CDCl_3) δ 165.10, 149.4, 138.91, 112.45, 77.05, 43.99, 34.75, 15.08; IR (neat) ν_{max} (C=O) 1775 cm^{-1} . *Anal.* calcd for $\text{C}_{12}\text{H}_{12}\text{F}_2\text{N}_2\text{O}_2\text{S}$: C, 50.34; H, 4.22; F, 13.27; N, 9.78; O, 11.18; S, 11.20. Found: C, 50.61; H, 4.34; F, 13.18; N, 9.87; O, 11.23; S, 11.13.

***N*-(1-(naphthalen-1-yl)ethyl)-2-oxo-4-(phenylthio)azetidine-1-carboxamide (65).**

— ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.97 (1H, d, $J=8.40$), 7.71 (1H, d, $J=7.85$), 7.62 (1H, d, $J=7.93$), 7.37 (3H, m), 7.10 (2H, s), 6.92 (2H, t, $J=6.53$), 6.71 (1H, d, $J=8.21$), 5.76 (1H, h, $J=7.21$), 5.05 (1H, dd, $J=2.74, 2.90$), 3.23 (1H, dd, $J=5.67, 10.71$), 2.72 (1H, dd, $J=2.72, 13.67$), 2.02 (3H, s), 1.57 (2H, d, $J=6.84$); ^{13}C NMR (125 MHz, CDCl_3) δ 165.36, 148.71, 138.17, 137.52, 133.95, 130.67, 128.93, 128.37, 125.82, 125.38, 124.92, 123.05, 122.46, 116.52, 57.30, 45.49, 44.08, 22.05; IR (neat) ν_{max} (C=O) $1772.15, 1700.24\text{ cm}^{-1}$. *Anal.* calcd for $\text{C}_{22}\text{H}_{19}\text{FN}_2\text{O}_2\text{S}$: C, 66.99; H, 4.86; F, 4.82; N, 7.10; O, 8.11; S, 8.13. Found: C, 67.19; H, 4.95; F, 4.79; N, 7.22; O, 8.12; S, 8.10.

2-((2,4-Difluorophenyl)Thio)-*N*-(2-Fluorobenzyl)-4-Oxoazetidine-1-Carboxamide (66).—Irradiated for 45minutes at specifications stated above for compound **61**. Purified by preparatory place on silica gel (2:1 Hexanes: Ethyl acetate) of the filtrate to give 34.3% yield.

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.44 (1H, dd, $J=6.51, 1.80$), 7.03 (2H, dt, $J=8.32, 8.30$), 6.69–6.87 (3H, m), 5.22 (1H, dd, $J=2.97, 2.62$), (1H, t, $J=6.54$), 3.4 (1H, dd, $J=10.81, 5.68$), 2.83 (1H, dd, $J=13.88, 2.62$); ^{13}C NMR (125 MHz, CDCl_3) δ 166.05, 162.37, 159.41, 157.24, 151.09, 131.35, 130.19, 129.60, 128.90, 122.07, 115.43, 111.27, 105.02, 63.30, 43.01, 38.95. IR (neat) ν_{max} (C=O) $1774, 1709\text{ cm}^{-1}$. *Anal.* calcd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2\text{S}$: C, 55.73; H, 3.58; F, 15.56; N, 7.65; O, 8.73; S, 8.75. Found: C, 55.93; H, 3.72; F, 15.67; N, 7.78; O, 8.79; S, 8.59.

2-((2,4-Difluorophenyl)Thio)-*N*-(2-Methoxybenzyl)-4-Oxoazetidine-1-Carboxamide (67).—Irradiated for 25minutes at specifications stated above for compound **61**.

Purified flash chromatography on silica gel with Hexanes:Ethylacetate = 1:1, and ethyl acetate to give 62.6% yield. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7–8.23, (3H, m), 5.15 (1H, dd, $J=2.48, 2.64$), 4.38 (1H, dd, $J=3.44, 2.67$), 3.78 (1H, s), 3.35 (1H, dd $J=10.73, 5.69$), 2.79 (1H, dd, $J=13.71, 2.69$), 1.19 (1H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 165.35, 164.87, 162.89, 162.24, 157.59, 149.35, 139.19, 129.60, 129.10, 125.86, 120.57, 112.43, 112.23, 110.32, 105.06, 104.80, 104.53, 56.30, 55.28, 39.75, 30.07; IR (neat) ν_{max} (C=O) $1775, 1700\text{ cm}^{-1}$. *Anal.* calcd for $\text{C}_{18}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_3\text{S}$: C, 57.14; H, 4.26; F, 10.04; N, 7.40; O, 12.68; S, 8.47. Found: C, 57.34; H, 4.32; F, 10.21; N, 7.51; O, 12.49; S, 8.37.

2-((2,4-Difluorophenyl)Thio)-*N*-(2-Fluorophenyl)-4-Oxoazetidine-1-Carboxamide (68).—After 10minutes of irradiated at specifications stated above for compound **61**.

The product was confirmed by NMR, but once solvent was evaporated, the product proved unstable. ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.5 (3H, m), 5.28 (1H, dd, $J=2.92, 2.75$), 3.47 (1H, dd, $J=10.84, 5.74$), 2.90 (1H, dd, $J=13.84, 2.75$).

2-((2,4-Difluorophenyl)Thio)-*N*-(2-Nitrobenzyl)-4-Oxoazetidine-1-Carboxamide (69).—The synthesis was performed as described by Mulchande et al.⁵ with the following modifications: 0.04mmol, 10mg of DL01 was dissolved in 1 mL of CDCl_3 with 1.5 mol eq.

of 2-nitrophenyl isocyanate. Then triethylamine (.001214g, .3 mol eq.) was added dropwise. The reaction was stirred, and monitored by NMR. It was confirmed the product was present after 30min, but out of solution when the solvent was removed product became unstable. No further analysis took place. ^1H NMR (400 MHz, CDCl_3) δ_{H} 3.39 (1H, dd, $J=10.72, 5.92$); 5.20 (1H, dd, $J=2.96, 2.91$); 7.4 (3H, m) 2.82 (1H, dd, $J=13.712, 2.93$).

***N*-benzhydryl-2-((2-chloro-4-fluorophenyl)thio)-4-oxoazetidine-1-carboxamide (70).**—Yield 30% MP waxy solid

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.56 (1H, dd, $J=6.01, 2.64$), 7.21 (5H, m), 6.80 (1H, dt, $J=2.73, 5.41$), 6.12 (1H, d, $J=8.65$), 5.25 (1H, dd, $J=2.78, 2.91$), 4.05 (1H, q, $J=7.12$), 3.42 (1H, dd, $J=5.72, 10.79$), 2.90 (1H, dd, $J=2.76, 13.74$), 1.97 (1H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 165.36, 164.36, 161.83, 148.72, 140.97, 140.10, 138.79, 128.80, 127.73, 127.32, 125.03, 117.92, 114.98, 57.29, 56.97, 44.08. IR (neat) ν_{max} (C=O) 1772.09, 1716.36 cm^{-1} . *Anal.* calcd for $\text{C}_{23}\text{H}_{18}\text{ClFN}_2\text{O}_2\text{S}$: C, 62.65; H, 4.12; Cl, 8.04; F, 4.31; N, 6.35; O, 7.26; S, 7.27. Found: C, 62.87; H, 4.22; Cl, 8.01; F, 4.39; N, 6.56; O, 7.21; S, 7.17.

Reaction of Lactam 34 with Sodium Hydroxide—Compound 34 was diluted to 1.0 mM in DMSO. The solution (3.0 mL) was placed in a quartz cuvette and a full range UV-Vis spectra was taken (800-200nm with 1.0 nm intervals). An initial peak was observed at $\lambda=256\text{nm}$. A 0.1 M solution of NaOH was then added dropwise. After each drop was added, the solution was mixed, allowed to incubate for 5 minutes, and then a full UV-Vis spectra was measured. The products of the reaction with NaOH showed a rising peak at $\lambda=345\text{nm}$.

Reaction of Lactam 34 with Penicillinase—Penicillinase was prepared at a 2.2 μM concentration in 100 mM sodium phosphate buffer. A full range UV-Vis spectra was taken of the penicillinase solution (2.95 mL). Following this, 50 μL of the 1.0 mM DL02 in DMSO was added with full range spectra taken at 5 minute intervals. No products of a hydrolysis of the four-membered β -lactam ring were detected.

4.2. Antimicrobial Assays

Antimicrobial activity for all isolates, with the exception of Mtb, was evaluated by B. J. Plotkin and J. M. Green (Midwestern University, Downers Grove, IL). All organisms used are listed in Table 4 and were maintained at $-80\text{ }^{\circ}\text{C}$. These bacteria with the exception of Mtb were provided by J. Thjio (Loyola University Stritch School of Medicine, Maywood, IL). The microdilution broth method was used to determine the minimal inhibitory concentrations and the minimum bactericidal concentrations (MIC/MBC).²⁰ All lactams were dissolved in dimethylsulfoxide (DMSO) then diluted at least 10 fold into Mueller-Hinton (MH) broth. Each diluted compound solution (100 μL /well) was then serially diluted in MH (100 μL /well; series of 2-fold dilutions, between 500 $\mu\text{g}/\text{mL}$ and 15.6 $\mu\text{g}/\text{mL}$). Controls consisted of 2-fold dilutions of DMSO alone. Bacteria were added to each well ($5\text{--}10^5$ cells/mL; 100 μL MH/well). After incubation ($37\text{ }^{\circ}\text{C}$; 48h) wells were scored for growth at 24h and 48h. The MIC was defined as the lowest concentration of drug at which no growth was observed. The MBC was determined as the lowest concentration of drug at

which no growth as measured by standard plating (10 μ L, MH agar) of wells where no growth was observed. All tests were performed in quadruplicate.

Mycobacterium tuberculosis (Mtb) H37Rv was used for all Mtb susceptibility determinations. These determinations were done by Kriti Arora (Tuberculosis Research Section, NIAID, NIH Bethesda, MD). Minimum inhibitory concentrations were determined by microdilution broth method as described previously.²¹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References:

1. Kostova MB; Myers CJ; Beck TN; Plotkin BJ; Green JM; Boshoff HM; Barry C, III; Deschamps J and Konaklieva MI, Bioorganic and Medicinal Chemistry, 2011, 19, 6842–6852. [PubMed: 22014754]
2. Clauss K; Grimm D; Prossel G, β -Lactame mit über Heteroatome gebundenen Substituenten. Justus Liebigs Annalen der Chemie 1974, 4, 539–560.
3. Wasserman HH X., M.; Carr AJ; Han WT; Siegel MG, Generation of Penems, Carbapenems and Aza Analogs of Cepems by the Addition of Heterocycles and Other Building Blocks to Azetionones. Tetrahedron 2000, 56, 5621–5629.
4. Mulchande J; Martins L; Moreira R; Archer M; Oliveira TF; Iley J, The Efficiency of C-4 Substituents in Activating the β -Lactam Scaffold towards Serine Proteases and Hydroxide ion. Org. Biomol. Chem 2007, 5 (16), 2617–26. [PubMed: 18019537]
5. Staub I; Sieber SA β -Lactams as Selective Chemical Probes for the in Vivo Labeling of Bacterial Enzymes Involved in Cell Wall Biosynthesis, Antibiotic Resistance, and Virulence. J. Am. Chem. Soc, 2008, 130 (40), 13400–13409. [PubMed: 18781750]
- 6 (a). Su Z; Peng L; Worthington R; Melander C, Evaluation of 4,5-disubstituted-2-aminoimidazole-triazole conjugates for antibiofilm/antibiotic resensitization activity against MRSA and *Acinetobacter baumannii*. ChemMedChem 2011, 6, 2243–2251; [PubMed: 21928438] (b) Rogers S; R. H., 3rd; Cavenagh J; Melander C, Synergistic effects between conventional antibiotics and 2-aminoimidazole-derived antibiofilm agents. Antimicrob Agents Chemother, 2010, 54, 2112–2118. [PubMed: 20211901]
7. Gu HZ, and Fedor LR Base-Catalyzed Elimination of *para*-Substituted Thiophenoxides from 4-(Arylthio)Azetidin-2-Ones." J. Org. Chem 1990, 55, 5655–5657.
8. Average of all thio-ethers in CSD which do NOT contain a cyclic S-atom (n=7154).
9. Average of all ethers in CSD which do NOT contain a cyclic O-atom (n>65,000).
10. Deziel R; Malenfant E Inhibition of human cytomegalovirus protease N(o) with monocyclic β -lactams. Bioorg. Med. Chem. Lett 1998, 8, 1437–1442. [PubMed: 9871780]
11. Bulychev A; Obrien ME; Massova I; Teng M; Gibson TA; Miller MJ and Mobashery S Potent Mechanism-Based Inhibition of the TEM-1 β -Lactamase by Novel N-Sulfonyloxy β -Lactams. J. Am. Chem. Soc, 1995, 117, 5938–5943.
12. Buynak JD; Chen HS; Vogeti L; Gadhachanda VR; Buchanan CA; Palzkill T; Shaw RW; Spencer J and Walsh TR Penicillin-Derived Inhibitors That Simultaneously Target Both Metallo- and Serine- β -Lactamases. Bioorg. Med. Chem. Lett 2004, 14, 1299–1304. [PubMed: 14980686]

13. Badarau A; Llinas A; Laws AP; Damblon C and Page MI Inhibitors of Metallo-Beta-Lactamase Generated from Beta-Lactam Antibiotics. *Biochemistry* 2005, 44, 8578–8589. [PubMed: 15952764]
- 14 (a). Opitz G; Koch J β -Amino β -Lactams *Angew. Chem., Int. Ed* 1963, 2, 152;(b)Perelman M; Mizak S J. *Am. Chem. Soc* 1962, 84, 4988–4989;(c)Nisole C; Uriac P; Toupet L; Huet J Ring Expansion of some 4-aminoazetidin-2-ones into 4-amino-5-iminopyrrolidin-2-ones *Tetrahedron* 1993, 49, 889–900.
- 15 (a). Alcaide B; Aly MF; Sierra MA Stereoselective Synthesis of 3-Substituted 4-(Formyloxy)-2-azetidinones by the Unusual Baeyer-Villiger Reaction of β -Lactam Aldehydes. Scope and Synthetic Applications *J. Org. Chem* 1996, 61, 8819–8825; [PubMed: 11667860] (b)Annunziata R; Benaglia M; Cinquini M; Cozzi F Stereoselective synthesis of 2-azetidinones as cholesterol-absorption inhibitors *Tetrahedron: Asymmetry* 1999, 10, 4841–4849.
- 16 (a). Effenberger F; Gleiter R *Chem. Ber* 1964, 97, 1576–1583;(b)Effenberger F; Kiefer G *Angew. Chem., Int. Ed* 1967, 6, 951–952;(c)Effenberger F; Fischer P; Prossel G; Kiefer G *Chem. Ber* 1971, 104, 1987–2001;(d)Effenberger F; Prossel G; Fischer P *Chem. Ber* 1971, 104, 2002–2012.
17. Furman B; Borsuk K; Kaluza Z; Lysek R and Chmielewski M Stereochemistry of [2+2] Cycloaddition of Chlorosulfonyl Isocyanate to Olefins, *Current Organic Chemistry*, 2004, 8, 463–473.
18. King FD; Caddick S The acid-mediated ring opening reactions of α -aryl-lactams. *Org. Biomol. Chem* 2012, 10, 3244–3252. [PubMed: 22406974]
19. Pardin C; Gillet SMFG and Keillor JW Synthesis and evaluation of peptidic irreversible inhibitors of tissue transglutaminase *Bioorganic and Medicinal Chemistry*, 2006, 14, 8379–8385. [PubMed: 17008102]
20. National Committee for Clinical Laboratory Standards, 1997.
21. Wong SY; Lee JS; Kwak HK, Via LE; Boshoff HI; Barry CE, III Mutations in *gidB* confer low-level streptomycin resistance in *Mycobacterium tuberculosis*. *Antimicrob. Agents. Chemother.*, 2011, 55, 2515–2522. [PubMed: 21444711]

Figure 1.
C4-arylthiolactams with antibacterial activity against Mtb and *M.cat*.

Figure 2: UV-Vis spectra of 2-(2,4-Difluoro-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide (**34**) after addition of NaOH. The mixture was incubated for 5 minutes after each drop of NaOH was added and the rise in peak height was most prominent at $\lambda=345\text{nm}$.

Figure 3:

The UV-Vis spectra of 2-(2,4-Difluoro-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide (**34**) during incubation with penicillinase. The compound and enzyme were incubated for 20 minutes with spectra taken at 5 minute intervals.

Scheme 1. Synthesis of N-substituted C4 arylthio-, aryloxy- and arylseleno-β-lactams.

a. β-Lactams **2 – 29** were prepared from the commercially available β-lactam **1** in the presence of NaHCO_3 in acetone/water ^{2,3}. **b.** β-Lactams **30-70**, excluding lactam **58** ($\text{R}_2 = \text{CO}(\text{CH}_2)_3\text{CCH}$) were prepared from β-lactams **2-29** using aryl isocyanates and Et_3N in methylene chloride at RT ⁴, or by using a CEM microwave apparatus at 300W, 30°C for 20-45minutes. Lactam **58** can be prepared from lactam **2** as described earlier.⁵

Scheme 2: Possible reaction pathways of the arylthio unsubstituted at N1 lactams with nucleophiles.

a.) “Classical” β -lactam nucleophilic attack on the lactam carbonyl carbon; phenoxide, ($\text{X}=\text{O}$), or thiophenoxide ($\text{X} = \text{S}$) or selenophenoxide ($\text{X} = \text{Se}$) as a leaving group. b) Deprotonation of the lactam nitrogen by a base, with departure of a suitable leaving group, i.e., a phenoxide, thiophenoxide or selenophenoxide, followed by protonation to phenol, thiol, or selenol, respectively. The formation of an imine *via* pathway a), as well as the formation of an acyliminium species, a possible Michael acceptor, in b), allows for a “double hit” mechanism by a second Nu, such as the active site cysteine in the Mtb glutaminase.

Scheme 3: Probable reaction pathway of the arylthio lactams leading to α,β -unsaturated amides. The opening of the ring is due to the electron-withdrawing substituent.¹⁷

Scheme 4: Probable reaction pathways of the carbamylated at N1 arylthio-lactams.
In addition to mechanisms **a)** described in Scheme 2; mechanism **b)** leads to generation of isocyanate.

Table 1.

Antimicrobial activity of C4-arylthio-, C4-arylseleno- and C4-aryloxy-, unsubstituted at N1, and N1-carbamylated β -lactams against Mtb and *M.cat* (n=6).

R ₁	#	R ₂	M.cat. ^a MIC/MBC μg/ml	Mtb without/with clavulanate MIC μg/ml	#	R ₂	M.cat. MIC/MBC μg/ml	Mtb without/with clavulanate MIC μg/ml
2	H	>200	25/25	30		12.5/12.5	6.25/6.25
3	H	200	25	31		25/50	3.13/3.13
4	H	>200	100/25	32		25/100	NT ^c
5	H	>200	>100/25	33		25/25	6.25/6.25
6	H	1.5/3.13	3.13/3.13	34		1.63/1.63	100/12.5
7	H	50/50	50/25	35		12.5/25	6.25/6.3

R ₁	#	R ₂	M.cat. ^a MIC/MBC μg/ml	Mtb without/with clavulanate MIC μg/ml	#	R ₂	M.cat. MIC/MBC μg/ml	Mtb without/with clavulanate MIC μg/ml
	8	H	1.5/1.5	>100	36		3.1/6.25	>100
	9	H	12.5/50	25	37		12.5/25	25-50
	10	H	12.5/25	25	38		6.25/6.25	25
	11	H	6.25/6.25	25	39		3.13/6.25	25
	12	H	6.25/12.5	25/25	40		3.125/25	25/25
	13	H	1.5/1.5	100	41		25/25	125
	14	H	200	6.25/12.5	42		3.125/6.25	25/6.25
	15	H	100/100	12.5/6.25	43		1.625/12.5	12.5/6.25

R ₁	#	R ₂	M.cat. ^a MIC/MBC μg/ml	Mtb without/with clavulanate MIC μg/ml	#	R ₂	M.cat. MIC/MBC μg/ml	Mtb without/with clavulanate MIC μg/ml
	16	H	12.5/100	>100	44		6.25/6.25	6.25/25
	17	H	100/>200	250/>250	45		200/200	125-250
	18	H	100/>200	>100	46		200/200	100
	19	H	200/>200	100	47		200/200	125
	20	H	100/>200	250	48		100/200	50
	21	H	200/200	250	49		200/>200	250
	22	H	25/100	6.25/12.5	50		50/100	6.25/6.25
	23	H	100/100	>100	51		NT	>100

R ₁	#	R ₂	M.cat. ^a MIC/MBC μg/ml	Mtb without/with clavulanate MIC μg/ml	#	R ₂	M.cat. MIC/MBC μg/ml	Mtb without/with clavulanate MIC μg/ml
	24	H	100/>200	>250	52		200/>200	>100
	25	H	50/50	25	53		6.25/6.25	250
	26	H	200/200	250	54		50/>200	125
	27	H	6.25/6.25	25	55		50/50	25
H	28	H	NT	NT	56		>100	>100
	29	H	>200	>200	57		NT/ chemically unstable	NT/ chemically unstable

^aThe values for *M. cat* are the results from the six isolates tested.

^bAll compounds are tested as racemates.

^cNT=not tested

Table 2.Antimicrobial activity of N1-carbamylated β -lactams against Mtb and *M. cat* (n=6).

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> </div> <div style="text-align: center;"> $R_1 = -S-\text{C}_6\text{H}_5$ (2,30,58-61) </div> <div style="text-align: center;"> $R_1 = -S-\text{C}_6\text{H}_4\text{F}$ (5,62,63) </div> </div>				
#	R ₂	<i>M.cat.</i> MIC/MBC $\mu\text{g/ml}$	Mtb without/ with clavulanate MIC $\mu\text{g/ml}$	
2	H	>200	25/ 25	
30		12.5/ 12.5	6.25/ 6.25	
58		100/ 100	45	
59		NT ^c	50	
60		NT	>100	
61		NT	25	
5	H	>200	>100/ 25	
62		>200/ >200	>100

#	R ₂	<i>M.cat.</i> MIC/ MBC μg/ml	Mtb without/ with clavulanate MIC μg/ml
63		>200/ >200	>100

^a The values for *M. cat* are the results from the six isolates tested.

^b All compounds are tested as racemates.

^c NT=not tested

Table 3.

Antimicrobial activity of fluorinated C4-arylthio-N1-carbamylated β -lactams against Mtb and *M.cat* (n=6).

#	R ₂	<i>M.cat.</i> MIC/MBC μg/ml	Mtb without/with clavulanate. MIC μg/ml	
6	H	1.5/3.13	3.13/3.13	
34		1.63/1.63	100/12.5	
64		NT ^c	>100/NT	
65		>200/>200	>100/NT	
66		NT	50/NT	
67		NT	100/NT	
68		NT	25	
69		NT Chemically unstable	NT Chemically unstable	
9	H	12.5/50	25

(6,34,64-69)		(9, 70)
#	R ₂	<i>M.cat.</i> MIC/ MB μg/ml	Mtb without/ with clavulanate. MIC μg/ml		
70		>200/ >200	50		

^a The values for *M.cat* are the results from the six isolates tested.

^b All compounds are tested as racemates.

^c NT=not tested

Table 4.

Organisms tested

Organism	Cell Wall Type	β -Lactamase Production
<i>Mycobacterium tuberculosis</i> H37R.V	Acid fast	BlaC
<i>Moraxella catarrhalis</i> 6 clinical isolates	Gram negative	BRO-1/BRO-2
<i>Staphylococcus aureus</i> ATCC 25923	Gram positive	None
<i>Escherichia coli</i> ATCC 25922	Gram negative	None
<i>Enterococcus faecalis</i> ATCC 29212	Gram positive	None
<i>Pseudomonas aeruginosa</i> ATCC 27853	Gram negative	None
<i>E. coli</i> MISC 206	Gram negative	Broad spectrum β -lactamases
<i>E. coli</i> GB 8	Gram negative	Broad spectrum β -lactamases
<i>E. coli</i> MISC 262	Gram negative	ESBL ^a
<i>Citrobacter freundii</i> Citro 314	Gram negative	ESBL
<i>Klebsiella pneumoniae</i> MISC 304	Gram negative	AmpC β -lactamase
<i>K. pneumoniae</i> KLEB 249	Gram negative	AmpC β -lactamase
<i>C. freundii</i> CITRO 21	Gram negative	AmpC β -lactamase
<i>Stenotrophomonas maltophilia</i> GM24	Gram negative	Metallo β -lactamases
<i>Acinetobacter baumannii</i> L185	Gram negative	ESBL & Carbapenase
<i>Acinetobacter baumannii</i> L186	Gram negative	ESBL & Carbapenase
<i>Acinetobacter baumannii</i> L187	Gram negative	ESBL & Carbapenase
KPC L133	Gram negative	ESBL & Carbapenase
<i>K. pneumoniae</i> /ESBL L174	Gram negative	ESBL & Carbapenase
<i>E. coli</i> ESBL L108	Gram negative	ESBL & Carbapenase
<i>E. coli</i> ESBL L109	Gram negative	ESBL & Carbapenase

^aESBL = extended spectrum β -lactamase

Table 5:

Comparison of bond lengths and bond angles of β -lactams with C4 thioethers described here, with known non-cyclic thioethers and ethers.

Compound	S-C(lac) Bond lengths	S-C(R1) Bond lengths	C-S-C Bond angles
2	1.803	1.773	102.37
22	1.816	1.748	102.24
	1.819	1.750	102.65
	1.819	1.750	102.64
Thio-ethers [6]	1.789	1.777	102.37
Ethers [7]	1.380	1.418	116.71