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Selective Synthesis of Ortho-substituted 3-Cyclohexyl-2-phenyl-1,3-thiazolidin-4-one Sulfoxides and Sulfones by *S*-Oxidation with Oxone

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Abstract

1,3-thiazolidin-4-ones, also known as thiazolidin-4-ones, are known to have a very wide range of biological activity. The corresponding *S*-oxides may show enhanced activity, and therefore viable synthetic routes to these *S*-oxides are required. *S*-oxidation of 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-ones with Oxone® was investigated. For all compounds evaluated, selective oxidation to the sulfoxide was realized using 3 equivalents of Oxone® at room temperature. Alternatively, the sulfone was prepared selectively at high temperature by increasing the equivalents of Oxone® used; the extent of this selectivity was affected by the substituent of the aromatic ring. In those cases in which the reaction produced a mixture of the sulfoxide and sulfone, the ratio of the products was quantified by ^{1}H NMR.

Keywords: Thiazolidin-4-ones, Oxone®, sulfoxide, sulfone

1. Introduction

1,3-thiazolidin-4-ones, also known as thiazolidin-4-ones, are known to have a very wide range of biological activity (Tripathi et al., 2014; Jain, Vaidya, Ravichandran, Kashaw, & Agrawal, 2012; Abhinit, Ghodke & Pratima, 2009; Hamama, Ismail, Shaaban & Zoorob, 2008; Singh, Parmar, Raman, Virgil & Stenberg, 1981; Brown, 1961), so much that some have referred to it as a "magic moiety" or "wonder nucleus" (Jain et al., 2012). The *S*-oxides may show enhanced activity; for example, Miller and coworkers converted one 4-thiazolidinone to its sulfoxide and sulfone and reported that the oxides showed greater activity against some cancer cell lines than the sulfide (Gududuru, Hurh, Dalton & Miller, 2004). Thiazolidin-4-ones have been oxidized to sulfoxides with peracetic acid (Surrey, 1967), Na_5IO_6 (Smith, Lee & Cragoe, 1977), chloramine T (Omar, El-Kharmy & Sharif, 1981), $NaIO_4$ (Lee, Yergatian, Crowther & Downie, 1990), Oxone® (one example, Rozwadowska, Sulima & Gzella, 2002), and *m*-CPBA (Rozwadowska & Sulima, 2003). Oxidation from sulfide to sulfoxide makes the sulfur a chiral center, and produces *cis* and *trans* diastereomers with relation to C-2 (Rozwadowska et al., 2002; Colombo et al., 2008). The stereocenters, however, may be configurationally unstable (Rozwadowska et al., 2002). Oxidation of thiazolidin-4-ones to sulfones has been accomplished with $H_2O_2/Ac_2O/AcOH$ (Troutman & Long, 1948), and $KMnO_4$ (Surrey, 1948).

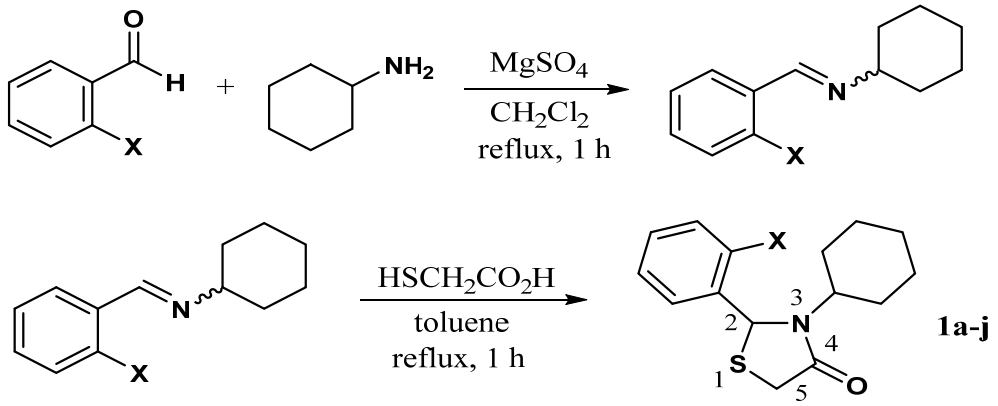
Oxone®, a mixture of potassium sulfates (2 $KHSO_5$/1 K_2SO_4/1 $KHSO_4$), is a very desirable material to use because it is a "green" reagent which is inexpensive, safe, and easy to use (Yu, et al., 2012; Hussain, Green & Ahmed, 2013). It has been used as a chemoselective reagent for the oxidation of sulfides to either sulfoxides (Trost & Curran, 1981; Yu, et al., 2012; Webb, 1994; Madesclaire, 1986) or sulfones (Trost & Curran, 1981; Yu, et al., 2012; Webb, 1994; Cannon, et al., 2013; Tierney, et al., 1996). Selectivity toward the sulfoxide or sulfone has been shown to depend on the amount of Oxone® used, the temperature, and the solvent (Trost & Curran, 1981; Yu, et al., 2012; Webb, 1994). Rozwadowska, et al. (2002) reported a single example of oxidation of a thiazolidin-4-one to its sulfoxide with this reagent.

We have previously reported the preparation of a series of *meta*- and *para*-substituted 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-ones (Cannon, et al., 2013; Tierney, et al., 1996). In this study, we report the preparation of a series of *ortho*-substituted 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-ones and show that Oxone® is a stronger oxidizer than $NaIO_4$ as evidenced by the higher yields of sulfone products for the parent and chloro-substituted thiazolidin-4-ones. We also report oxidations of the full series of the *ortho*-substituted thiazolidin-4-ones with Oxone® and $KMnO_4$ to prepare a series of novel thiazolidin-4-one *S*-oxides and to ascertain the scope and selectivity of the Oxone® oxidations.

2. Results and Discussion

2.1 Preparation of Ortho-substituted Thiazolidin-4-ones

The *ortho*-substituted 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-ones **1a-j** (Table 1) were prepared by the conversion of the respective *ortho*-substituted benzaldehyde to the cyclohexyl imine, followed by condensation with thioglycolic acid (Scheme 1) (Cannon, et al., 2013; Tierney, et al., 1996).



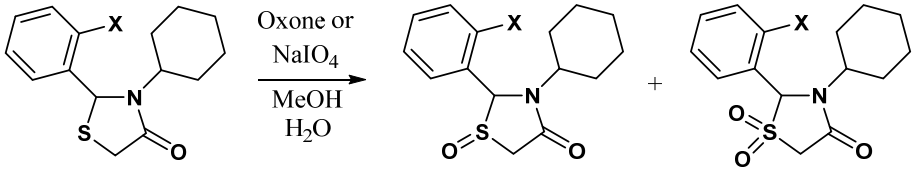
Scheme 1. Synthesis of *ortho*-substituted 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-ones **1a-j**

Table 1. *Ortho*-substituted 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-ones **1a-1j** synthesized according to Scheme 1.

Product	% Yield	Melting Point (°C)	R_f (3:1 cyclohexane:EtOAc)
1a, X = H	64	115-116	0.524
1b, X = Cl	58	101-102	0.710
1c, X = F	75	87-89	0.685
1d, X = Br	44	110-111	0.713
1e, X = CH_3	58	68-70	0.599
1f, X = CF_3	60	91-92	0.539
1g, X = OCH_3	43	oil	0.607
1h, X = OCH_2CH_3	73	100-101	0.663
1i, X = NO_2	36	109-110	0.377
1j, X = 1-naphthyl	80	108-109	0.662

2.2 Evaluation of Oxone® vs. $NaIO_4$ toward Thiazolidin-4-one Oxidation

Since both Oxone® and $NaIO_4$ have been previously reported to oxidize thiazolidin-4-ones to the corresponding sulfoxides (Rozwadowska, et al., 2002; Rozwadowska & Sulima, 2003), both oxidants were evaluated for yield and selectivity by reacting **1a** and **1b** (Scheme 2) with 8 equivalents of oxidant both at room temperature and at aqueous methanol reflux. At the end of the indicated reaction time, the product mixture was checked by thin layer chromatography (TLC) for unreacted thiazolidin-4-one, which was absent in all cases. TLC also indicated only two reaction products. Proton nuclear magnetic resonance (^{1}H NMR) analysis of the compounds extracted from the aqueous MeOH product solutions confirmed these results. Integration of the C2 proton resonances for the resulting sulfoxide and sulfone in each trial provided the relative ratios of these two products, and combined percent yields were calculated based upon these ratios. The results of this preliminary evaluation are reported in Table 2.



1a: X = H
1b: X = Cl

2a, 2b **3a, 3c**

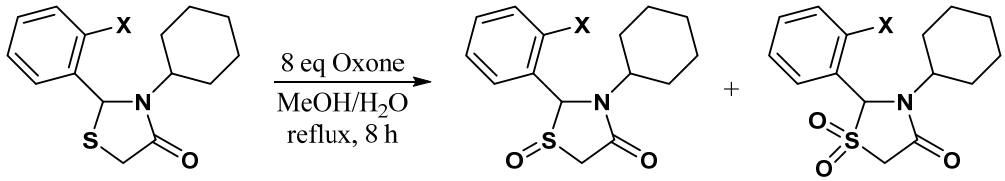
Scheme 2. Oxidation of thiazolidin-4-ones using Oxone® and $NaIO_4$

Table 2. Comparison of thiazolidin-4-one *S*-oxidations of 1a and 1b by Oxone® and $NaIO_4$. The ratio indicates the relative amounts of sulfoxide to sulfone as determined by ^{1}H NMR.

Reaction Conditions	Oxidation of 1a 2a:3a (total yield)	Oxidation of 1b 2b:3b (total yield)
8 eq Oxone, aq. MeOH, rt, 20.5 h	3.3:1.0 (94 %)	6.1:1.0 (99 %)
8 eq $NaIO_4$, aq. MeOH, rt, 20.5 h	33:1.0 (100 %)	51:1.0 (98 %)
8 eq Oxone, aq. MeOH, reflux, 8 h	1.0:3.2 (93 %)	1.0:1.2 (98 %)
8 eq $NaIO_4$, aq. MeOH, reflux, 8 h	3.3:1.0 (93 %)	8.2:1.0 (71 %)

2.3 High Temperature Oxone® Oxidations of Thiazolidin-4-ones

Under both general reaction conditions, complete conversion of **1a** and **1b** was realized with both reagents, but Oxone® demonstrated a greater propensity for sulfone formation (**3a** and **3b**, respectively). Additionally, **1a** and **1b** produced different ratios of sulfoxide and sulfone products, suggesting that the ratio is a function of the substituent of the C2 aromatic ring. We therefore oxidized compounds **1c-j** according to the high temperature Oxone-based reaction conditions to determine if selective formation of either sulfoxide or sulfone could be realized according to the substituted aromatic ring (Scheme 3). Results including the oxidation of compounds **1a** and **1b** are presented in Table 3.



1a-j **2a-j** **3a-j**

Scheme 3. Oxidation of thiazolidin-4-ones using high temperature Oxone®-based reaction conditions

Results in Table 3 show that Oxone® *S*-oxidation of thiazolidin-4-ones varied as a function of the C2 substituted aromatic ring. However, no clear substitution/reactivity correlation could be ascertained. The lowest Oxone® reactivity was observed for halide-substituted compounds **1b-1d**, with the fluoro- and bromo-substituted thiazolidin-4-ones yielding greater amounts of sulfoxide versus sulfone under the described reaction conditions. In contrast, alkoxy-substituted (**1g** and **1h**) and nitro-substituted (**1i**) thiazolidin-4-ones yielded the respective sulfone exclusively. Both the unsubstituted (**1a**) and methyl-substituted (**1e**) thiazolidin-4-ones exhibited a strong preference for sulfone formation, with the remaining compounds showing a diminished preference for sulfone formation.

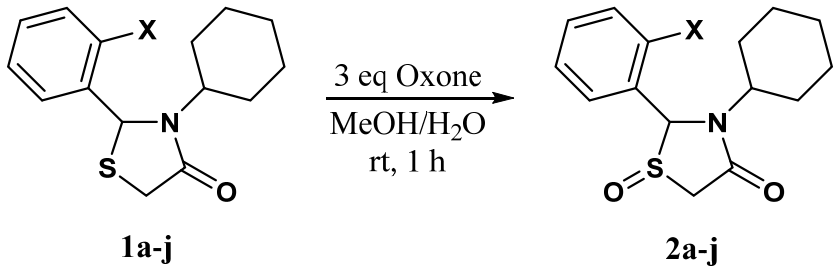
Table 3. Oxidation of thiazolidin-4-ones **1a-1j** using high temperature Oxone®-based reaction conditions. The ratio indicates the relative amounts of sulfoxide to sulfone as determined by ^{1}H NMR analysis of the isolated product mixture.

Thiazolidin-4-one (1)	Sulfoxide:Sulfone (2:3)	Total Yield
1a, X = H	1.0:3.2	93 %
1b, X = Cl	1.0:1.2	98 %
1c, X = F	2.0:1.0	95 %
1d, X = Br	2.1:1.0	88 %
1e, X = CH_3	1.0:4.9	75 % *
1f, X = CF_3	1.0:1.7	89 %
1g, X = OCH_3	Sulfone only	98 % *
1h, X = OCH_2CH_3	Sulfone only	66 % *
1i, X = NO_2	Sulfone only	94 % *
1j, X = 1-naphthyl	0.76:1.0	90 %

Note. * indicates an isolated yield.

2.4 Low Temperature Oxone® Oxidations of Thiazolidin-4-ones

Exclusive formation of sulfoxide compounds **2a**-**2j** was realized by performing the oxidation at room temperature with a reduced number of Oxone® equivalents (Scheme 4). The reaction time for sulfoxide formation was optimized at 1h to insure complete conversion of the thiazolidin-4-ones. Results are summarized in Table 4. Oxidation of **1a** at extended reaction times showed no sulfone formation at periods as long as 45 h.



1a-j **2a-j**

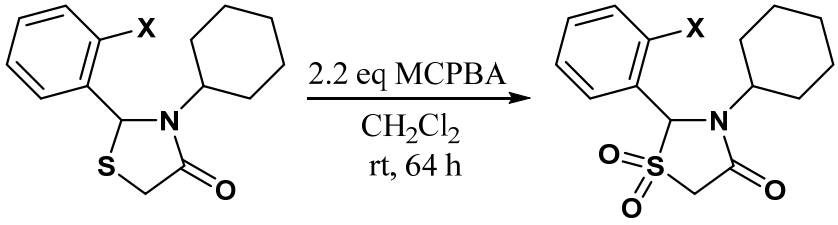
Scheme 4. Selective Oxone® oxidation of thiazolidin-4-ones to sulfoxides

2.5 MCPBA- and $KMnO_4$-based Oxidations of Thiazolidin-4-ones

Since exclusive formation of *ortho*-substituted 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-one sulfones was not reliably realized using Oxone®, alternative syntheses of the sulfones were evaluated. Although MCPBA had been reported to yield sulfoxides selectively (Rozwadowska & Sulima, 2003), we found that reaction of **1a** and **1b** with 2.2 equivalents of MCPBA at room temperature yielded sulfones **3a** and **3b** in excellent yields (Scheme 5).

Table 4. *Ortho*-substituted 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-one sulfoxides 2a-2j synthesized according to Scheme 4.

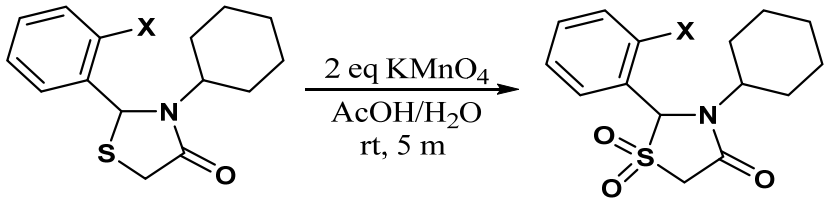
Product	% Yield	Melting Point (°C)	R_f (3:1 cyclohexane:EtOAc)
2a, X = H	96	177-178	0.118
2b, X = Cl	97	140-142	0.164
2c, X = F	91	171-172	0.177
2d, X = Br	94	148-149	0.297
2e, X = CH_3	96	179-180	0.140
2f, X = CF_3	95	135-136	0.117
2g, X = OCH_3	92	142-143	0.0714
2h, X = OCH_2CH_3	91	119-120	0.100
2i, X = NO_2	96	oil	0.0741
2j, X = 1-naphthyl	78	175-176	0.129



1a, X = H **3a,** 99 %
1b, X = Cl **3b,** 93 %

Scheme 5. MCPBA oxidation of thiazolidin-4-ones to sulfones

A much faster although lower yielding transformation of thiazolidin-4-ones to sulfones was described by Surrey (1948) using aqueous $KMnO_4$. This method was applied to compounds **1a**-**1j** to produce the corresponding sulfones (Scheme 6); results are summarized in Table 5.



1a-j **3a-j**

Scheme 6. $KMnO_4$ oxidation of thiazolidin-4-ones to sulfones

Table 5. *Ortho*-substituted 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-one sulfones 3a-3j synthesized according to Scheme 6.

Product	% Yield	Melting Point (^oC)
3a, X = H	64	115-116
3b, X = Cl	58	101-102
3c, X = F	75	87-89
3d, X = Br	44	110-111
3e, X = CH_3	42	68-70
3f, X = CF_3	60	91-92
3g, X = OCH_3	43	Oil, R_f = 0.329
3h, X = OCH_2CH_3	73	100-101, R_f = 0.336
3i, X = NO_2	64	198-199
3j, X = 1-naphthyl	67	108-109

Note. R_f values correspond to 3:1 cyclohexane:EtOAc.

3. Conclusion

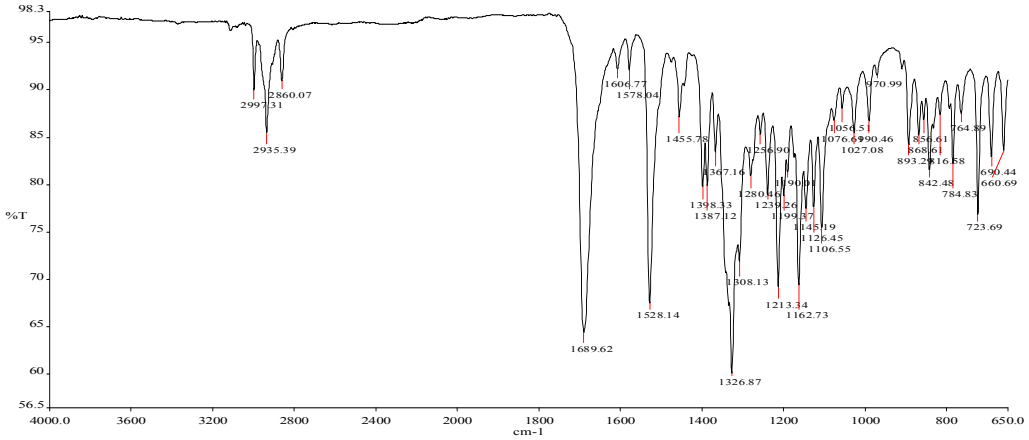
S-oxidation of 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-ones with Oxone® was dependent on the reaction temperature, equivalents of Oxone® used, and the substituent on the aromatic ring of the thiazolidin-4-one. For all thiazolidin-4-ones evaluated, selective oxidation to the sulfoxide was realized by using 3 equivalents of Oxone® at room temperature; reaction time under these conditions did not impact selectivity. By increasing the amount of Oxone® to 8 equivalents, room temperature oxidation of two thiazolidin-4-ones (**1a** and **1b**) resulted in the formation of sulfone as a significant byproduct. At high temperature using 8 equivalents of Oxone®, the extent of reaction selectivity was affected by the substituent on the aromatic ring, although no clear substituent/reactivity correlation was evident. Exclusive formation of the sulfone vs. the sulfoxide was realized by oxidation of thiazolidin-4-one using either 2 equivalents of $KMnO_4$ (sulfones **3a-j**) or 2.2 equivalents of MCPBA (sulfones **3a** and **3b**).

4. Experimental

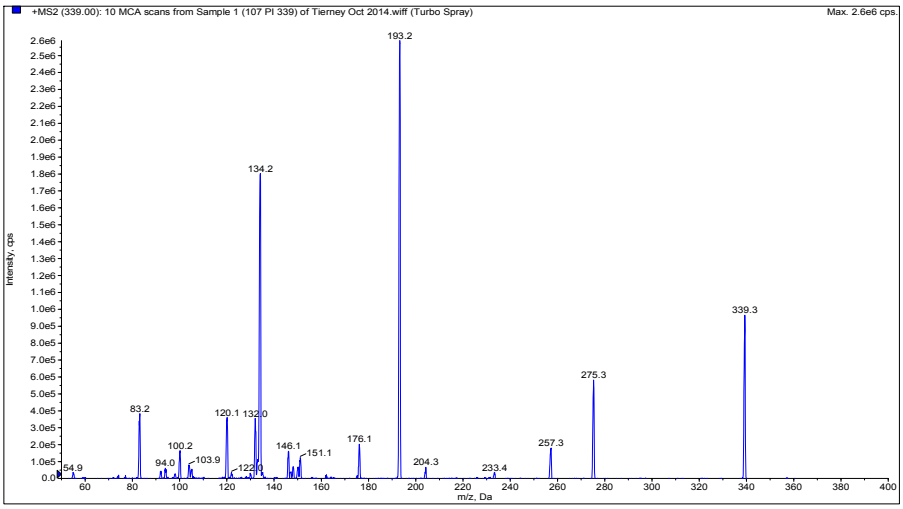
Reagent chemicals were obtained from commercial suppliers; Oxone® was purchased from Aldrich Chemical Company. TLC and chromatography plates (silica gel GF, 250 micron) were purchased from Analtech. Reagent grade solvents were used without further purification.

Most spectra were recorded on a Bruker 400 at 298K observing ^1H and ^{13}C at 300.15 and 75.48 MHz, respectively. These samples were dissolved in $CDCl_3$ at a concentration of 100 mg/mL using precision bore 5 mm NMR tubes supplied by Norell, Inc. The spectrometer was locked to either the deuterium or carbon resonance of $CDCl_3$ and all chemical shifts were referenced to residual $CHCl_3$. One high temperature ^1H NMR spectrum (340K) was recorded on a Bruker DRX 500 observing ^1H at 500 MHz. The sample was dissolved in C_6D_6 at a concentration of 50 mg/mL. The spectrometer was locked to the deuterium resonance of C_6D_6 and all chemical shifts were referenced to residual C_6H_6.

Infrared spectra were obtained as an evaporated thin film on a sodium chloride plate (Janos Technology, Inc) on a Nicolet Nexus 670 spectrometer using 32 scans at a 2 cm^{-1} resolution. Mass spectra were recorded on a Varian 2100 G ion trap mass spectrometer, fitted with a Varian 3900 gas chromatograph: column - Factor 4 VF-5ms 0.25 mm id, 30 m, 0.25 μm film thickness, He carrier gas, 1.0 ml/min flow, 80°C for 1 minute isothermal 15°C/min to 275°C then 275°C for 3 minutes isothermal, injector temp 250°C, 0 min, 1:50 split. Melting points are uncorrected; a Uni-Melt capillary melting point apparatus was used. An example of both FTIR and mass spectra are shown below for sulfone-3-cyclohexyl-2-(2-nitrophenyl)-1,3-thiazolidin-4-one (**3i**).



FTIR of **3i**



Mass spectrum of **3i**

4.1 Preparation of Ortho-substituted Thiazolidin-4-ones

Thiazolidine-4-ones were prepared using the procedure previously described. (Cannon, et al., 2013; Tierney, et al., 1996) Isolated yields are based on starting amounts for the imines (amine is the limiting reactant) and it was assumed that 100% of the imine was produced *in situ*. No attempt was made to maximize the product yields. Products were purified by recrystallization using methanol, or by chromatography on precoated plates of silica gel GF 250 µm using 3:1 cyclohexane/EtOAc.

3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-one (**1a**). Yield (64%); R_f = 0.524; m.p. 115-116 ^oC, IR: cm^{-1} 1658.6 (C=O); ^1H NMR ($CDCl_3$): 7.39-7.28 (5H, m, aromatics), 5.65 (1H, d, C2, J = 1.8 Hz), 3.91 (1H, dd, C5, J = 1.9 Hz and J = 15.5 Hz), 3.82 (1H, m, NCH), 3.61 (1H, d, C5, J = 15.4 Hz), 1.79-0.90 (10H, m, cyclohexyls); ^{13}C NMR: 171.94 (C4), 130.161, 129.28, 129.07, 126.47, 62.83 (C2), 56.28, 33.47 (C5), 31.28, 30.32, 26.24, 25.58; MS: (m/z) 261 (M^+), $C_{15}H_{19}ONS$ (261.12).

2-(2-chlorophenyl)-3-cyclohexyl-1,3-thiazolidin-4-one (**1b**). Yield (58%); R_f = 0.710; m.p. 101-2^oC; IR: cm^{-1} 1665.1 (C=O); ^1H NMR ($CDCl_3$): 7.38-7.22 (4H, m, aromatics), 6.08 (1H, C2), 3.94 (1H, tt, J = 12.2 Hz, and J = 3.4 Hz, NCH), 3.79 (1H, d, C5, J = 15.3 Hz), 3.53 (1H, d, C5, J = 15.3 Hz), 1.91-0.91 (10H, m, cyclohexyls); ^{13}C NMR: 172.51 (C4), 140.18, 131.63, 130.24, 129.49, 127.35, 126.86, 58.14 (C2), 55.80, 32.64 (C5), 31.17, 30.40, 25.99, 25.90, 25.36; MS: (m/z) 295 (M^+), $C_{15}H_{18}ONSCl$ (295.08).

3-cyclohexyl-2-(2-fluorophenyl)-1,3-thiazolidin-4-one (**1c**). Yield (75%); R_f = 0.685; m.p. 87-89 ^oC; IR: cm^{-1} 1665.0 (C=O); ^1H NMR ($CDCl_3$): 7.31-7.04 (4H, m, aromatics), 5.91 (1H, d, C2, J=1.5 Hz), 3.89 (1H, tt, J = 12.1 Hz, and J = 3.3 Hz, NCH), 3.88 (1H, dd, C5, J=1.5 Hz and J=15.6 Hz), 3.56 (1H, d, C5, J = 15.4 Hz), 1.77-0.86 (10H, m, cyclohexyls); ^{13}C NMR: 171.81 (C4), 159.74 (d, J=266.4 Hz), 130.28 (m),127.70, 124.59, 116.30, 116.13, 55.93 (C2), 55.83, 33.12 (C5), 30.88, 30.14, 25.96, 25.36; MS: (m/z) 279 (M^+), $C_{15}H_{18}ONSF$

(279.11).

2-(2-bromophenyl)-3-cyclohexyl-1,3-thiazolidin-4-one (**1d**). Yield (44%); R_f = 0.713; m.p. 110-111 ^oC; IR: cm^{-1} 1664.0 (C=O); ^1H NMR ($CDCl_3$): 7.57-7.15 (4H, m, aromatics), 6.05 (1H, C2), 3.94 (1H, tt, J = 12.1 Hz, and J = 3.4 Hz, NCH), 3.78 (1H, d, C5, J = 15.5 Hz), 3.52 (1H, d, C5, J = 15.5 Hz), 1.84-0.92 (10H, m, cyclohexyls); ^{13}C NMR: 172.67 (C4), 141.76, 133.41, 129.73, 127.98, 126.81, 121.64, 60.82 (C2), 55.80, 33.43 (C5), 31.30, 30.48, 25.99, 25.89, 25.36. MS: (m/z) 339 (M^+), $C_{15}H_{18}ONSBr$ (339.03).

3-cyclohexyl-2-(2-methylphenyl)-1,3-thiazolidin-4-one (**1e**). Yield (58%); R_f = 0.599; m.p. 68-70 ^oC; IR: cm^{-1} 1657.4 (C=O); ^1H NMR ($CDCl_3$): 7.25-7.12 (4H, m, aromatics), 5.85 (1H, C2), 3.84 (1H, t(br), J = 11.9 Hz, NCH), 3.76 (1H, dd, C5, J = 1.6 Hz and J = 15.4 Hz), 3.50 (1H, d(br), C5, J = 15.3 Hz), 2.35 (3 H, s, CH_3), 1.81-0.91(10H, m, cyclohexyls).^{13}C NMR: 172.14 (C4), 140.17, 133.67, 131.06, 128.11, 126.40, 125.14, 58.20 (C2), 55.81, 32.61 (C5), 30.78, 30.17, 25.85, 25.84, 25.28, 18.96; MS: (m/z) 275 (M^+), $C_{16}H_{21}ONS$ (275.13).

3-cyclohexyl-2-(2-trifluoromethylphenyl)-1,3-thiazolidin-4-one (**1f**). Yield: (60%); R_f = 0.539; m.p. 91-92 ^oC; IR: cm^{-1} 1680.5 (C=O); ^1H NMR ($CDCl_3$): 7.61-7.34 (4H, m, aromatics), 6.00 (1H, C2), 3.87 (1H, tt, J = 12.4 Hz, and J = 3.6 Hz, NCH), 3.79 (1H, dd, C5, J = 1.5 Hz, and J = 15.6 Hz), 3.49 (1H, C5, J = 15.6 Hz), 1.72-0.94 (10H, m, cyclohexyls) ; ^{13}C NMR: 172.28 (C4), 142.40 (d, J = 1.3 Hz), 132.55, 128.21, 126.59, 126.17 (q, J = 6.0 Hz), 125.71 (q, J = 30.1 Hz), 124.30 (q, J = 274.6 Hz), 56.89 (q, J = 2.7 Hz, C2), 55.84, 32.32 (C5), 31.00, 30.02, 25.90, 25.76, 25.19; MS: (m/z) 329 (M^+), $C_{16}H_{18}ONSF_3$ (329.11).

3-cyclohexyl-2-(2-methoxyphenyl)-1,3-thiazolidin-4-one (**1g**). Yield (43%); R_f = 0.607; oil; IR: cm^{-1} 1658.5 (C=O); ^1H NMR ($CDCl_3$): 7.28-6.86 (4H, m, aromatics), 5.94 (1H, C2), 3.89-3.82 (4H, m, 1H/NCH and 3H/CH_3, (3.84)), 3.77 (1H, d, C5, J = 15.3 Hz), 3.46 (1H, d, C5, J = 15.3 Hz), 1.76-0.88 (10H, m, cyclohexyls).^{13}C NMR: 172.31 (C4), 156.05, 130.65, 129.40, 126.36(br) , 120.50, 111.02, 56.82(br, C2), 55.51, 33.10 (C5), 30.57, 30.00, 25.82, 25.27; MS: (m/z) 291 (M^+), $C_{16}H_{21}O_2NS$ (291.13).

3-cyclohexyl-2-(2-ethoxyphenyl)-1,3-thiazolidin-4-one (**1h**). Yield (73%); R_f = 0.663; m.p. 100-101 ^oC; IR: cm^{-1} 1666.9 (C=O); ^1H NMR ($CDCl_3$): 7.28-6.83 (4H, m, aromatics), 5.96 (1H, s(vbr), C2), 4.14-3.77 (4H, m, overlapping OCH_2/NCH/C5), 3.46 (1H, d, CH_2, J = 15.1 Hz), 1.42 (3 H, t, CH_3, J = 6.9 Hz), 1.74-0.87 (10H, m, cyclohexyls). ^{13}C NMR: 172.24 (C4), 155.58(br), 130.65, 129.42, 126.58(br), 120.35, 111.90, 63.80 (C2), 55.52, 32.23(br, C5), 30.50, 29.96, 25.86, 25.32, 14.82; MS: (m/z) 305 (M^+), $C_{17}H_{23}O_2NS$ (305.14).

3-cyclohexyl-2-(2-nitrophenyl)-1,3-thiazolidin-4-one (**1i**). Yield (64%); R_f = 0.377; IR: cm^{-1} 1671.1 (C=O); ^1H NMR ($CDCl_3$): 8.08-7.46 (4H, m, aromatics), 6.25 (1H, C2), 3.94 (1H, tt, J = 12.2 Hz, and J = 3.6 Hz, NCH), 3.76 (1H, dd, C5, J = 0.7 Hz, and J = 15.7 Hz), 3.47 (1H, d, C5, J = 15.7 Hz), 1.96-0.86 (10H, m, cyclohexyls); ^{13}C NMR: 172.95 (C4), 146.05, 139.12, 134.02, 129.04, 126.72, 125.68, 58.82 (C2), 55.74, 32.20(C5), 31.25, 30.29, 25.89, 25.70, 25.19; MS: (m/z) 306(M^+) $C_{15}H_{18}O_3N_2S$ (306.10).

3-cyclohexyl-2-(1-naphthyl)-1,3-thiazolidin-4-one (**1j**). Yield (80 %); R_f = 0.662; m.p. 108-109 ^oC; IR: cm^{-1} 1695.3, 1668.7 (C=O); ^1H NMR ($CDCl_3$): 7.94-7.46 (7H, m, aromatics), 6.46 (1H, C2), 4.02 (1H, m, NCH), 3.82 (1H, d(br), C5, J = 15.0 Hz), 3.57 (1H, d(br), C5, J = 14.8 Hz), 1.98-0.89 (10H, m, cyclohexyls); ^{13}C NMR: 173.24 (C4), 137.56, 134.22, 129.47, 129.26, 128.91, 127.03, 126.30, 125.32, 122.06, 121.83, 57.54 (C2), 55.80, 33.21 (C5), 31.17, 30.50, 26.00, 25.90, 25.27; MS: (m/z) 311 (M^+), $C_{19}H_{21}ONS$ (311.13).

4.2 General Procedure for the RT Synthesis of Thiazolidin-4-one Sulfoxides via Oxone®

Thiazolidin-4-one (1.01 mmol) was dissolved in methanol (8.0 mL), to which an aqueous solution of Oxone® (461 mg, 3.03 mmol calculated as $KHSO_5$, 152.2 g mol^{-1}, in 4.0 mL water) was added dropwise at room temperature with vigorous stirring. After the addition, the reaction mixture was stirred for 1 h. Water (40 mL) was then added to the mixture to dissolve precipitates, and the mixture was extracted with $CHCl_3$ (4 x 10 mL). The combined $CHCl_3$ layers were dried with Na_2SO_4, and the $CHCl_3$ was removed *in vacuo* followed by chromatography.

Sulfoxide-3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-one (**2a**). Yield (96%); R_f = 0.118; m.p. 177-178 ^oC: IR: cm^{-1} 1667.5 (C=O), 1051.4 (S=O); ^1H NMR ($CDCl_3$): 7.42-7.29 (5H, m, aromatics), 5.57 (1H, s, C2), 4.20 (1H, tt, J = 12.2 Hz, and J = 3.7 Hz, NCH), 3.74 (1H, d, J = 16.9 Hz, C5), 3.30 (1H, d, J = 16.9 Hz, C5), 1.89-1.23 (10H, m, cyclohexyls); ^{13}C NMR: 169.33 (C4), 132.52, 129.75, 129.61, 126.46, 82.92, 54.67, 52.25, 31.70, 30.31, 25.80, 25.49, 25.30. MS: (m/z) 277 (M^+), $C_{15}H_{19}O_2NS$ (277.11).

Sulfoxide-2-(2-chlorophenyl)-3-cyclohexyl-1,3-thiazolidin-4-one (2b). Yield (97%); R_f = 0.164; m.p. 140.5-142 ^oC; IR: cm^{-1} 1677.9 (C=O), 1057.2, 1050.2 (S=O); ^1H NMR ($CDCl_3$): 7.46 (1H, d, J = 8.0 Hz), 7.35-7.27 (2H, m, aromatics), 7.15 (1 H, d, J = 7.6 Hz), 5.83 (1H, s, C2), 4.19 (1H, tt, J = 12.1 Hz, and J = 3.2 Hz, NCH), 3.60 (1H, d, J = 3.6 Hz, C5), 3.30 (1H, dd, J = 17.0, and J = 2.9 Hz, C5), 1.88-1.21 (10H, m,

cyclohexyls); ^{13}C NMR: 169.92 (C4), 133.38, 130.93, 130.64,129.87, 127.63, 126.99, 79.95, 54.58, 52.38, 31.47, 30.20, 25.70, 25.35, 25.15; MS: (m/z) 311 (M^+), $C_{15}H_{18}O_2NSCl$ (311.07).

Sulfoxide-3-cyclohexyl-2-(2-fluorophenyl)-1,3-thiazolidin-4-one (**2c**). Yield (91%); R_f = 0.177; m.p. 171-172 ^oC; IR: cm^{-1} 1671.5 (C=O), 1036.0 (S=O); ^{1}H NMR ($CDCl_3$): 7.39-7.19 (4H, m, aromatics), 5.76 (1H, br s, C2), 4.20 (1H, tt, J = 12.4 Hz, and J = 3.6 Hz, NCH), 3.69 (1H, d, J = 16.8 Hz, C5), 3.36 (1H, dd, J = 16.4 Hz, and J = 0.8 Hz, C5), 1.97-0.91 (10H, m, cyclohexyls); ^{13}C NMR: 169.2 (C4), 159.5 (d, J = 248.3 Hz), 131.4 (d, J = 7.1 Hz), 126.7 (d, J = 1.6 Hz), 124.7 (d, J = 3.1 Hz), 119.6 (d, J = 12.9 Hz), 116.1 (d, J = 20.6 Hz), 76.3, 54.0, 52.2, 31.1, 29.8, 25.3, 25.0, 24.8; MS: (m/z) 295 (M^+), $C_{15}H_{18}O_2NSF$ (295.10).

Sulfoxide-2-(2-bromophenyl)-3-cyclohexyl-1,3-thiazolidin-4-one (**2d**). Yield (94%); R_f = 0.297; m.p. 148-149 ^oC; IR: cm^{-1} 1682.9 (C=O), 1060.3 (S=O); ^{1}H NMR ($CDCl_3$): 7.66 (1H, dd, J = 8.0, and J = 1.2 Hz, aromatic), 7.35 (1 H, ddd, J = 8.0, 8.0, 1.2 Hz, aromatic), 7.25 (1 H, ddd, J = 8.0, 8.0, 1.2 Hz, aromatic), 7.14 (1H, dd, J = 8.0, 1.2 Hz, aromatic), 5.81 (1H, s, C2), 4.21 (1H, tt, J = 12.0 Hz, and J = 3.6 Hz, NCH), 3.60 (1H, d, J = 16.8 Hz, C5), 3.32 (1H, dd, J = 16.8 Hz, and J = 0.8 Hz, C5), 1.85-0.82 (10H, m, cyclohexyls); ^{13}C NMR: 169.91 (C4), 133.80, 131.54, 131.40, 128.05, 12702, 123.40, 81.91, 54.26, 52.02, 31.34, 30.03, 25.50, 25.12, 24.94. MS: (m/z) 356 (M^+), $C_{15}H_{18}O_2NSBr$ (355.02).

Sulfoxide-3-cyclohexyl-2-(2-methylphenyl)-1,3-thiazolidin-4-one (**2e**). Yield (96%); R_f = 0.140; m.p. 178-179 ^oC; IR: cm^{-1} 1686.3 (C=O), 1051.1 (S=O); ^{1}H NMR ($CDCl_3$): 7.32-7.06 (4H, m, aromatics), 5.65 (1H, s, C2), 4.20 (1H, br tt, J = 12.0 Hz, and J = 3.2 Hz, NCH), 3.70 (1H, d, J = 16.8 Hz, C5), 3.29 (1H, d, J = 16.8 Hz, C5), 2.57 (3 H, s, CH_3), 1.92-0.87 (10H, m, cyclohexyls).^{13}C NMR: 169.24 (C4), 135.45, 131.19, 129.37, 129.22, 126.48, 124.77, 79.64, 53.95 (C2), 51.82, 31.09 (C5), 29.93, 25.26, 24.96, 24.80, 19.10; MS: (m/z) 291 (M^+), $C_{16}H_{21}O_2NS$ (291.13).

Sulfoxide-3-cyclohexyl-2-(2-trifluoromethylphenyl)-1,3-thiazolidin-4-one (**2f**). Yield: (95%); R_f = 0.117; m.p. 135-136 ^oC; IR cm^{-1} 1672.2 (C=O), 1064.9, 1033.9 (S=O); ^{1}H NMR ($CDCl_3$), 7.76 (1H, d, J = 7.6 Hz), 7.56 (1H, br dd, J = 7.2 Hz, and J = 6.8 Hz), 7.49 (1H, br dd, J = 7.6 Hz, and J = 7.6 Hz), 7.23 (1H, d, J = 7.6 Hz), 5.73 (1H, s, C2), 4.17 (1H, tt, J = 12.0 Hz, and J = 3.6 Hz, NCH), 3.79 (1H, d, J = 17.2 Hz, C5), 3.34 (1H, d, J=17.2 Hz, C5), 1.86-1.24 (10H, m, cyclohexyls) ; ^{13}C NMR: 169.50 (C4), 132.64, 130.90, 129.82, 127.34 (q, J = 30.5 Hz), 127.43 (q, J = 5.6 Hz), 126.73, 122.44 (q, J = 271.8 Hz)**,** 79.01, 54.49, 51.76, 31.47, 29.91, 25.47, 25.22, 25.04; MS: (m/z) 345 (M^+), $C_{16}H_{18}O_2NSF_3$ (345.10).

Sulfoxide-3-cyclohexyl-2-(2-methoxyphenyl)-1,3-thiazolidin-4-one (**2g**). Yield (92%); R_f = 0.0714; m.p. 142-143 ^oC; IR: cm^{-1} 1673.2 C=O), 1056.5 (S=O); ^{1}H NMR ($CDCl_3$): 7.33-6.91 (4H, m, aromatics), 5.79 (1H, s, C2), 4.17 (1H, tt, J = 12.4 Hz, and J = 3.6 Hz, NCH), 3.92 (3H, s, CH_3), 3.57 (1H, d, J = 16.8 Hz), 3.21 (1H, dd, J = 16.8 Hz, and J = 0.8 Hz, C5), 1.86-1.24 (10H, m, cyclohexyls). ^{13}C NMR: 169.70 (C4), 156.25, 130.78, 126.01, 120.68, 119.75, 110.68, 77.47, 55.54, 54.02, 52.31, 31.06, 29.90, 25.42, 25.12, 24.91; MS: (m/z) 307 (M^+), $C_{16}H_{21}O_3NS$ (307.12).

Sulfoxide-3-cyclohexyl-2-(3-ethoxyphenyl)-1,3-thiazolidin-4-one (**2h**). Yield (91%); R_f = 0.100; m.p. 119-120 ^oC; IR: cm^{-1} 1677.5 (C=O), 1058.2, 1038.4 (S=O); ^{1}H NMR ($CDCl_3$): 7.29-7.02 (4H, m, aromatics), 5.75 (1H, s, C2), 4.13 (3H, m, OCH_2, and NCH), 3.54 (1 H, d, J = 16.8 Hz, C5), 3.19 (1 H, brd, J = 16.8 Hz, C5), 1.45 (3 H, t, J = 7.2 Hz, CH_3), 1.73-0.88 (10H, m, cyclohexyls). ^{13}C-NMR: 169.67 (C4), 155.61, 130.65, 126.03, 120.45, 119.71, 111.43, 77.70, 63.94, 53.96, 52.36, 30.95, 29.85, 25.38, 25.08, 24.86, 14.50; MS: (m/z) 321 (M^+), $C_{17}H_{23}O_3NS$ (321.14).

Sulfoxide-3-cyclohexyl-2-(2-nitrophenyl)-1,3-thiazolidin-4-one (**2i**). Yield (96%); oil, R_f = 0.0741; IR: cm^{-1} 1678.5 (C=O), 1057.9 (br, S=O); ^{1}H NMR ($CDCl_3$): 8.30 (1H, dd, J = 8.0 Hz, and J = 1.2 Hz, aromatic), 7.73 (1 H, ddd, J = 7.6 Hz, J = 7.6 Hz, and J = 1.2 Hz, aromatic), 7.63 (1 H, ddd, J = 7.6 Hz, J = 7.6 Hz, and J = 1.2 Hz, aromatic), 7.60 (1H, m, aromatic), 6.21 (1H, s, C2), 4.23 (1H, tt, J = 12.0 Hz, and J = 3.6 Hz, NCH), 3.60 (1H, d, J = 16.8 Hz, C5), 3.38 (1H, dd, J = 16.8 Hz, and J = 0.8 Hz, C5), 1.89-1.35 (10H, m, cyclohexyls); ^{13}C NMR: 170.38 (C4), 146.57, 134.67, 130.80, 128.75, 127.58, 126.65, 78.91, 54.48 (C2), 52.05, 31.26 (C5), 29.90, 25.51, 25.10, 24.88; MS: (m/z) 322 (M^+) $C_{15}H_{18}O_4N_2S$ (322.10).

Sulfoxide-3-cyclohexyl-2-(1-naphthyl)-1,3-thiazolidin-4-one (**2j**). Yield (78%); R_f = 0.129; m.p. 174-175 ^oC; IR: cm^{-1} 1682.9 (C=O), 1057.6 (S=O); ^{1}H NMR ($CDCl_3$): 8.23-7.38 (7 H, m, aromatics), 6.25 (1H, s, C2), 4.33 (1 H, tt, J = 12.0 Hz, and J = 3.6 Hz, NCH), 3.70 (1 H, d, J = 16.8 Hz, C5), 3.39 (1 H, dd, J = 16.8 Hz, and 0.8 Hz, C5), 1.83-0.94 (10 H, m, cyclohexyls); ^{13}C-NMR: 169.98 (C4), 133.92, 130.55, 129.81, 129.46, 127.86, 127.04, 126.84, 125.10, 123.94, 121.67, 79.80, 54.58, 53.95, 31.39, 30.26, 25.60, 25.30, 25.07; MS: (m/z) 327 (M^+), $C_{19}H_{21}O_2NS$ (327.13).

4.3 General Procedure for the Synthesis of Thiazolidin-4-one Sulfones via $KMnO_4$

Thiazolidin-4-one (0.553 mmol) was dissolved in glacial acetic acid (2.4 mL), to which an aqueous solution of $KMnO_4$ (175 mg, 1.11 mmol, in 3.0 mL water) was added dropwise at room temperature with vigorous stirring, and stirred an additional 5 m. Solid sodium bisulfite ($NaHSO_3/Na_2S_2O_5$) was then added until the solution remained colorless; 3.0 mL of water was then added to the mixture and stirred for 10 m. Most crude products were isolated as powders by filtration and water rinses; products were purified by recrystallization in CH_3OH. Products **3g** and **3h** were not isolated as powders, but rather by extraction of the reaction mixture with toluene (3 x 10 mL). The combined toluene layers were dried with Na_2SO_4, and toluene was removed *in vacuo* followed by chromatography.

Sulfone-3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-one (**3a**). Yield (64%); m.p. 115-116 ^oC; IR: cm^{-1} 1676.8 (C=O), 1317.2, 1135.9 (S=O); ^1H NMR ($CDCl_3$): 7.49-7.32 (5H, m, aromatics), 5.52 (1H, s, C2), 4.33 (1 H, brt, J = 12.3 Hz, NCH), 3.84 (1H, d, J = 16.6 Hz, C5), 3.75 (1H, d, J = 16.0 Hz, C5), 1.92-0.90 (10H, m, cyclohexyls); ^{13}C NMR: 163.05 (C4), 132.02, 130.50, 129.46, 127.19, 79.74, 54.35, 50.06, 31.60, 29.86, 25.65, 25.43, 25.10. MS: (m/z) 294 ($[M+H]^+$), $C_{15}H_{19}O_3NS$ (293.11).

Sulfone-2-(2-chlorophenyl)-3-cyclohexyl-1,3-thiazolidin-4-one (3b). Yield (58%); m.p. 101-2 ^oC; IR: cm^{-1} 1682.9 (C=O), 1333.3, 1137.0 (S=O); ^1H NMR ($CDCl_3$): 7.47 (1 H, d, J = 7.6 Hz), 7.36-7.28 (2H, m, aromatics), 7.20 (1 H, d, J = 7.6 Hz), 6.04 (1H, s, C2), 4.28 (1H, tt, J = 12.2 Hz, and J = 3.2 Hz, NCH), 3.77 (1H, d, J=16.4 Hz, C5), 3.67 (1H, d, J = 16.3 Hz, C5), 1.87-0.74 (10H, m, cyclohexyls); ^{13}C NMR: 163.23 (C4), 134.76, 131.57, 130.88, 130.23, 127.63, 126.63, 76.47, 54.35, 50.28, 31.69, 29.92, 25.64, 25.38, 25.06; MS: (m/z) 328 ($[M+H]^+$), $C_{15}H_{18}O_3NSCl$ (327.07).

Sulfone-3-cyclohexyl-2-(2-fluorophenyl)-1,3-thiazolidin-4-one (**3c**). Yield (75%); m.p. 87-89 ^oC; IR: cm^{-1} 1683.5 (C=O), 1332.7, 1136.7 (S=O); ^1H NMR ($CDCl_3$): 7.41-7.09 (4H, m, aromatics), 5.67 (1H, s, C2), 4.23 (1H, tt, J = 12.0 Hz, and J = 4.8 Hz, NCH), 3.78 (1H, d, J = 16.4 Hz, C5), 3.68 (1H, d, J = 16.4 Hz, C5), 1.81-0.74 (10H, m, cyclohexyls); ^{13}C NMR: 163.01 (C4), 161.16 (d, J=249.3 Hz), 132.51 (d, J = 8.0 Hz),127.97 (br), 125.04 (d, J = 2.6 Hz), 120.30 (d, J = 12.5 Hz), 116.80 (d, J = 21.4 Hz), 74.90 (br), 54.27, 50.76, 31.38, 29.81, 25.64, 25.45, 25.10; MS: (m/z) 312 ($[M+H]^+$), $C_{15}H_{18}O_3NSF$ (311.10).

Sulfone-2-(2-bromophenyl)-3-cyclohexyl-1,3-thiazolidin-4-one (**3d**). Yield (44%); m.p. 110-111 ^oC; IR: cm^{-1} 1692.6 (C=O), 1328.3, 1161.9 (S=O); ^1H NMR ($CDCl_3$): 7.66-7.16 (4H, m, aromatics), 6.05 (1H, s, C2), 4.29 (1H, brt, J = 12.0 Hz, NCH), 3.78 (1H, d, J = 16.2 Hz, C5), 3.52 (1H, d, J = 16.9 Hz, C5), 1.88-0.73 (10H, m, cyclohexyls); ^{13}C NMR: 163.11 (C4), 134.19, 131.79, 128.23, 126.87, 124.83, 78.91, 54.35, 50.31, 31.73, 29.96, 25.65, 25.38, 25.07. MS: (m/z) 372 ($[M+H]^+$), $C_{15}H_{18}O_3NSBr$ (371.02).

Sulfone-3-cyclohexyl-2-(2-methylphenyl)-1,3-thiazolidin-4-one (**3e**). Yield (42%); m.p. 68-70 ^oC; IR: cm^{-1} 1683.7 (C=O), 1325.9, 1306.9, 1128.7 (S=O); ^1H NMR ($CDCl_3$): 7.26 (3H, m, aromatic), 7.10 (1H, m, aromatic), 5.69 (1 H, s, C2), 4.26 (1 H, tt, J = 12.0, and J = 3.6 Hz, NCH), 3.78 (1 H, d, J = 16.0 Hz, C5), 3.63 (1 H, d, J = 16.4 Hz, C5), 2.60 (3 H, s, CH_3), 1.89-1.16 (10 H, m, cyclohexyls); ^{13}C NMR: 163.08 (C4), 137.33, 131.66, 130.04, 126.64, 124.71, 76.5,2 54.15, 49.91, 31.50, 29.89, 25.48, 25.25, 24.99, 19.86; MS: (m/z) 308 ($[M+H]^+$), $C_{16}H_{21}O_3NS$ (307.12).

Sulfone -3-cyclohexyl-2-(2-trifluoromethylphenyl)-1,3-thiazolidin-4-one (**3f**). Yield: (60%); m.p. 91-92 ^oC; IR: cm^{-1} 1683.5 (C=O), 1341.0, 1304.6, 1119.2, 1107.1 (S=O); ^1H NMR ($CDCl_3$): 7.84 (1H, d, J = 7.7 Hz), 7.64 (2H, dt, J = 31.0 Hz, and J = 7.5 Hz), 7.43 (1H, d, J = 7.8 Hz), 5.96 (1H, s, C2), 4.39 (1H, tt, J = 12.3 Hz, and J = 3.4 Hz, NCH), 3.91 (1H, d, J = 16.3 Hz, C5), 3.82 (1H, d, J = 16.8 Hz, C5), 1.92-0.79 (10H, m, cyclohexyls) ; ^{13}C NMR: 163.10 (C4), 132.84, 131.35, 130.62, 129.34 (q, J = 30.9 Hz), 127.53 (q, J = 5.4 Hz), 126.83, 123.88 (q, J = 273.7 Hz), 76.19, 54.47, 50.26, 31.77, 29.81, 25.77, 25.48, 25.14; MS: (m/z) 362 ($[M+H]^+$), $C_{16}H_{18}O_3NSF_3$ (361.10).

Sulfone-3-cyclohexyl-2-(2-methoxyphenyl)-1,3-thiazolidin-4-one (**3g**). Yield (43%); oil, R_f = 0.329; IR: cm^{-1} 1686.4 (C=O), 1332.1, 1126.5 (S=O); ^1H NMR ($CDCl_3$): 7.45-7.00 (4H, m, aromatics), 6.06 (1H, br s, C2), 4.32 (1H, br m, NCH), 3.92 (3 H, s, CH_3), 3.80 (1H, br d, J = 14.9 Hz), 3.67 (1H, br d, J = 15.0 Hz, C5), 1.91-0.88 (10H, m, cyclohexyls); ^{13}C NMR: 163.51 (C4), 158.03, 131.70, 125.65, 120.97, 120.66, 111.70, 74.17, 56.03, 54.25, 50.15, 31.50, 29.84, 25.69, 25.51, 25.18; MS: (m/z) 324 ($[M+H]^+$), $C_{16}H_{21}O_4NS$ (323.12).

Sulfone-3-cyclohexyl-2-(3-ethoxyphenyl)-1,3-thiazolidin-4-one (**3h**). Yield (73%); R_f = 0.336; m.p. 100-101 ^oC; IR: cm^{-1} 1695.8 (C=O), 1334.6, 1329.1, 1162.7 (S=O); ^1H NMR, 400 MHz, rt, ($CDCl_3$): 7.28-6.83 (4H, m, aromatics), 5.96 (1H, s(vbr), C2), 4.14-3.77 (4H, m, overlapping OCH_2/NCH/C5), 3.46 (1H, d, CH_2, J = 15.1 Hz), 1.42 (3 H, t, CH_3, J = 6.9 Hz), 1.74-0.87 (10H, m, cyclohexyls); ^1H NMR, 500 MHz, 67 ^oC, (C_6D_6): 7.19

(1H, t, J = 5.8 Hz), 7.06 (1H, s(br)), 6.86 (1H, t, J = 6.0 Hz), 6.70 (1H, d, J = 6.8 Hz), 6.13 (1H, s(vbr), C2), 4.30 (1H, br t, J = 8.8 Hz), 3.82 (2H, br q, J = 5.6 Hz, OCH_2), 3.52 (1H, br s, NCH), 3.39 (1H, br d, J = 12.0 Hz, C5), 1.27 (3H, t, CH_3, J = 5.2 Hz), 1.83-0.74 (10H, m, cyclohexyls). ^{13}C NMR: 172.24 (C4), 155.58(br), 130.65, 129.42, 126.58(br), 120.35, 111.90, 63.80 (C2), 55.52, 32.23(br, C5), 30.50, 29.96, 25.86, 25.32, 14.82; MS: (m/z) 338 ($[M+H]^+$), $C_{17}H_{23}O_4NS$ (337.13).

Sulfone-3-cyclohexyl-2-(2-nitrophenyl)-1,3-thiazolidin-4-one (**3i**). Yield (64%); m.p. 198-199 ^oC; IR: cm^{-1} 1689.6 (C=O), 1326.9, 1308.1, 1162.7 (S=O); ^1H NMR ($CDCl_3$): 8.38 (1H, dd, J = 8.0, and J = 1.2 Hz, aromatic), 7.78 (1 H, dddd, J = 8.0, 8.0, 1.2, 0.8 Hz, aromatic), 7.68 (1 H, ddd, J = 8.0, 8.0, 1.2 Hz, aromatic), 7.54 (1H, dd, J = 7.6, 1.2 Hz, aromatic), 6.77 (1 H, s, C2), 4.41 (1 H, tt, J = 12.0, and J = 3.6 Hz, NCH), 3.76 (dd, J = 16.0 Hz, and J = 0.4 Hz, 1H), 3.69 (d, J = 16.4 Hz, 1 H), 1.96-0.82 (10 H, m, cyclohexyls); ^{13}C NMR: 163.41 (C4), 147.80, 134.43, 131.22, 128.82, 126.92 75.77, 54.52, 50.16, 31.39, 29.67, 25.50, 25.16, 24.84; MS: (m/z) 339 ($[M+H]^+$) $C_{15}H_{18}O_5N_2S$ (338.09).

Sulfone-3-cyclohexyl-2-(1-naphthyl)-1,3-thiazolidin-4-one (**3j**). Yield (67%); m.p. 108-109 ^oC; IR: cm^{-1} 1666.4 (C=O), 1368.4, 1329.2, 1162.4 (S=O); ^1H NMR ($CDCl_3$): 8.07-7.39 (7H, m, aromatics), 6.40 (1H, C2), 4.42 (1H, tt, J = 12.2 Hz, and J = 3.6 Hz, NCH), 3.95 (1H, d, J = 16.4 Hz, C5), 3.76 (1H, d, J = 16.2 Hz, C5), 2.04-0.85 (10H, m, cyclohexyls); ^{13}C NMR: 163.54 (C4), 134.14, 131.32, 131.19, 129.45, 127.76, 127.70, 126.89, 125.01, 123.80, 122.42, 76.22, 54.62, 49.87, 31.41, 29.97, 25.61, 25.42, 25.02; MS: (m/z) 344 ($[M+H]^+$), $C_{19}H_{21}O_3NS$ (343.12).

*4.4 High temperature oxidation of thiazolidin-4-ones **1a-j** using Oxone®*

Thiazolidin-4-one **1a-j** (0.103 mmol) was dissolved in MeOH (16 mL), to which a solution of Oxone® (1.251 g, 0.824 mmol, in 8 mL H_2O) was added dropwise at room temperature with vigorous stirring. Then the reaction mixture was heated to reflux for 8 h. Upon cooling, 40 mL of H_2O was added and the solution was then extracted with CH_2Cl_2 (3 x 25 mL). The combined CH_2Cl_2 layers were dried with Na_2SO_4, and the CH_2Cl_2 was removed *in vacuo*. The resulting product was dissolved in $CDCl_3$ and analyzed by ^1H NMR. The molar ratio of sulfoxide **2** to sulfone **3** was determined by the average of three integrations of the respective C2 protons.

*4.5 High temperature oxidation of thiazolidin-4-ones **1a-b** using $NaIO_4$*

Thiazolidin-4-one **1a-b** (0.319 mmol) was dissolved in MeOH (6.5 mL), to which a solution of $NaIO_4$ (546 mg, 2.55 mmol, in 75 % (v/v) aq. MeOH (28 mL), was added dropwise at room temperature with vigorous stirring. Then the reaction mixture was heated to reflux for 8 h. Upon cooling, the reaction mixture was filtered and the solvent was removed *in vacuo*. H_2O (20 mL) was added and the solution was then extracted with CH_2Cl_2 (3 x 15 mL). The combined CH_2Cl_2 layers were dried with Na_2SO_4, and the CH_2Cl_2 was removed *in vacuo*. The resulting product was dissolved in $CDCl_3$ and analyzed by ^1H NMR. The molar ratio of sulfoxide **2** to sulfone **3** was determined by the average of three integrations of the respective C2 protons.

*4.6 Oxidation of thiazolidin-4-one **1a** to sulfone **3a** using MCPBA.*

Thiazolidin-4-one **1a** (0.534 mmol) was dissolved in CH_2Cl_2 (4 mL), to which a solution of MCPBA (404 mg, 1.17 mmol, in 7 mL CH_2Cl_2) was added dropwise at room temperature with vigorous stirring. The reaction mixture was allowed to stir at rt for 64 h. The reaction mixture was filtered to separate precipitated *m*-chlorobenzoic acid, and the solution was then extracted with sat. $NaHCO_3$ (4 x 10 mL) and H_2O (10 mL). The CH_2Cl_2 layer was dried with Na_2SO_4, and the CH_2Cl_2 was removed *in vacuo*. Recrystallization of the resulting white foam in CH_3OH produced 154 mg (99 %) of sulfone **3a**.

*4.7 Oxidation of thiazolidin-4-one **1b** to sulfone **3b** using MCPBA.*

Thiazolidin-4-one **1b** (0.404 mmol) was dissolved in CH_2Cl_2 (3 mL), to which a solution of MCPBA (307 mg, 0.889 mmol, in 6 mL CH_2Cl_2) was added dropwise at room temperature with vigorous stirring. The reaction mixture was allowed to stir at rt for 64 h. The reaction mixture was filtered to separate precipitated *m*-chlorobenzoic acid, and the solution was then extracted with sat. $NaHCO_3$ (4 x 10 mL) and H_2O (10 mL). The CH_2Cl_2 layer was dried with Na_2SO_4, and the CH_2Cl_2 was removed *in vacuo*. Recrystallization of the resulting white foam in CH_3OH produced 123 mg (93 %) of sulfone **3b**.

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References

Abhinit, M., Ghodke, M., & Pratima, N. A. (2009). Exploring potential of 4-thiazolidinone: a brief review. *Int. J. Pharmacy Pharm. Sci. 1*, 47-64.

Brown, F. C. (1961). 4-Thiazolidinones. *Chem. Rev.*, *61*, 463-521. http://dx.doi.org/10.1021/cr60213a002

Cannon, K., Mascavage, L., Tierney, J., Kistler, K., Yennawar, H., & Lagalante, A. (2013). Verifying the predictability of ^{13}C chemical shifts for a series of substituted-2-(4-chlorophenyl)-3-phenyl-1,3-thiazolidin-4-ones. *Intl. J. Chem*., *5* (3), 46-56. http://dx.doi.org/10.5539/ijc.v5n3p46

Colombo, A., Fernandez, J. C., Fernandez-Forner, D., de la Figuera, N., Albericio, F., & Forns, P. (2008). Stereomeric studies on the oxidation and alkylation of 4-thiazolidinones. *Tet. Lett.*, *49*, 1569-72. http://dx.doi.org/10.1016/j.tetlet.2008.01.038

Gududuru, V., Hurh, E., Dalton, J. T., & Miller, D. D. (2004). Discovery of 2-arylthiazolidine-4-carboxylic acid amides as a new class of cytotoxic agents for prostate cancer. *Bioorg. Med. Chem. Lett.*, *14*, 5289-93. http://dx.doi.org/10.1016/j.bmcl.2004.08.029

Hamama, W. S., Ismail, M. A., Shaaban, S., & Zoorob, H. H. (2008). Progress in the chemistry of 4-thioazolidinones. *J. Het. Chem.*, *45*, 939-56. http://dx.doi.org/10.1002/jhet.5570450401

Hussain, H., Green, I. R., & Ahmed, I. (2013). Journey describing applications of oxone in synthetic chemistry. Chem. Rev., 113, 3329−3371. http://dx.doi.org/10.1021/cr3004373

Jain, A. K., Vaidya, A., Ravichandran, V., Kashaw, S. K., & Agrawal, R. A. (2012). Recent developments and biological activities of thiazolidinone derivatives: a review. Bioorg. Med. Chem., 20, 3378-95. http://dx.doi.org/10.1016/j.bmc.2012.03.069

Lee, J. B., Yergatian, S. Y., Crowther, B. C., & Downie, I. M. (1990). Preparation of 4-thiazolidinone 1-oxides. *Org. Prep. Proc. Int.*, *22*, 544-6. http://dx.doi.org/10.1080/00304949009356324

Madesclaire, M. (1986). Reduction of sulfoxides to thioethers. *Tetrahedron, 42*, 5459-80. http://dx.doi.org/10.1016/S0040-4020(01)88150-3

Omar, M. T., El-Kharmry, A. E., & Sherif, F. A. (1981). Synthesis of 2,3-disubstituted-4-oxothiazolidine 1-oxides. J. Het. Chem., 18, 633-4. http://dx.doi.org/10.1002/jhet.5570180311

Rozwadowska, M. D., & Sulima, A. (2003). Studies of some hydrogenated thiazolo[2,3-a]isoquinoline S-oxides. Tetrahedron, 59, 1173-9. http://dx.doi.org/10.1016/S0040-4020(03)00023-1

Rozwadowska, M. D., Sulima, A., & Gzellla, A. (2002). Synthesis, crystal structure and oxidation of (R)-(+)-8,9-dimethoxy-6,10b-dihydro-5H-thiazolo[2,3-a]isoquinolin-3-one. Tet. Asymm., 13, 2329-33. http://dx.doi.org/10.1016/S0957-4166(02)00633-X

Singh, S. P., Parmar, S. S., Raman, R., Virgil I., & Stenberg, V. I. (1981). Chemistry and biological activity of thiazolidinones. Chem. Rev., 81, 175-203. http://dx.doi.org/10.1021/cr00042a003

Smith, R. L., Lee, T. J., & Cragoe, E. J. (1977). Certain thiazolidine compounds. U.S. Patent 4059587.

Surrey, A. R. (1948). The preparation of 2,3-disubstituted-4-thiazolidones. II. 3-Alkyl (and aralkyl) 2-aryl derivatives. J. Am. Chem. Soc., 70, 4262-3. http://dx.doi.org/10.1021/ja01192a515

Surrey, A. R. (1967). 3-[(2-Oxazolidinone-3-yl)-alkyl]-4-thiazolidinones and their preparation. U.S. Patent 3309377.

Tierney, J., Houghton, G., Sanford, K., Mascavage, L., McCoy, M., Findeisen, A. J., & Kilburn, J. (1996). Effects and conformational analysis of some substituted 2,3-diphenyl-1,3-thiazolidin-4-ones. Magn. Reson. Chem., 34, 573-6 .http://dx.doi.org/10.1002/(SICI)1097-458X(199608)34:8%3C573::AID-OMR928%3E3.3.CO;2-4

Tripathi, A. C., Gupta, S. J., Fatima, G. N., Sonar, P. K., Verma, A., & Saraf, S. K. (2014). 4-Thiazolidinones: the advances continue…. Eur. J. Med. Chem., 72, 52-77. http://dx.doi.org/10.1016/j.ejmech.2013.11.017

Trost, B. M., & Curran, D. P. (1981). Chemoselective oxidation of sulfides to sulfones with potassium hydrogen persulfate. Tet. Lett., 22, 1287-90. http://dx.doi.org/10.1016/S0040-4039(01)92384-6

Troutman, H. D., & Long, L. M. (1948). The synthesis of 2,3-disubstituted-4-thiazolidones. J. Am. Chem. Soc., 70, 3436-9. http://dx.doi.org/10.1021/ja01190a064

Webb, K. S. (1994). A mild, inexpensive and practical oxidation of sulfides. Tet. Lett., 35, 3457-60. http://dx.doi.org/10.1016/S0040-4039(00)73209-6

Yu, B., Liu, A. H., He, L. N., Li, B., Diao, Z. F., & Li, Y. N. (2012). Catalyst-free approach for solvent-dependent selective oxidation of organic sulfides with oxone. Green Chem., *14*, 957. http://dx.doi.org/10.1039/c2gc00027j