International Journal of Chemistry; Vol. 8, No. 2; 2016
ISSN 1916-9698 E-ISSN 1916-9701
Published by Canadian Center of Science and Education

A Study of ^{13}C Chemical Shifts for a Series of 2-(4-methoxyphenyl)-substituted-3-phenyl-1,3-thiazolidin-4-ones

Chino Mannikarottu[1], John Tierney[1], Kevin C. Cannon[2], Linda Mascavage[3], Anthony Lagalante[4]

[1]Department of Chemistry, Pennsylvania State University, Brandywine Campus, Media, PA 19063, USA

[2]Department of Chemistry, Pennsylvania State University, Abington Campus, Abington, PA 19001, USA

[3]Department of Chemistry, Arcadia University, Glenside, PA, 19038, USA

[4]Department of Chemistry, Villanova University, 800 Lancaster Avenue, Villanova, PA 19085, USA

Correspondence: Kevin C. Cannon, Department of Chemistry, 1600 Woodland Road, Penn State Abington College, Abington, PA, 19001, USA. Tel: 215-881-7468. E-mail: kcc10@psu.edu

Received: March 15, 2016 Accepted: April 5, 2016 Online Published: April 13, 2016

doi:10.5539/ijc.v8n2p43 URL: http://dx.doi.org/10.5539/ijc.v8n2p43

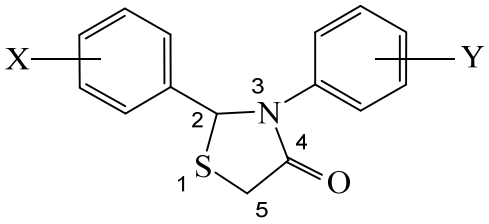
Abstract

The ^{13}C substituent chemical shifts C-2, C-4 and C-5 (with a particular focus at C-2) for disubstituted 2,3-diphenylthiazolidin-4-ones with one substituent in each phenyl ring are systematically being investigated. The substituents in question are *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *p*-Br, *m*-Br, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3 and *m*-OCH_3. This combination of substituents leads to a 13 x 13 matrix array of compounds with the fixed substituents in the 2-phenyl ring constituting the columns and the fixed substituents in the 3-phenyl rings constituting the rows. Including this present study, 81 of the total 169 compounds in the matrix have been analyzed. A single *para*-methoxy group interacting with another fixed substituent, as measured by ^{13}C substituent chemical shift values at C-2 in either the C-2 phenyl or N-3 phenyl rings, shows little deviation. This changes however when the moiety is either an alkyl group at N-3 or when a *para*-methoxy group is the fixed substituent on the N-3 phenyl ring. This present study shows that a *para*-methoxy group on a C-2 phenyl ring shows a similar deviation in the efficacy in the transmission of electronic effects witnessed in this set of matrix compounds and mimics the issues seen with a previously studied *para*-methoxy substituted system with the *para*-methoxy group on the N-3 phenyl ring. Reasons for these aberrations are discussed.

Keywords: thiazolidin-4-one, ^{13}C NMR, Hammett

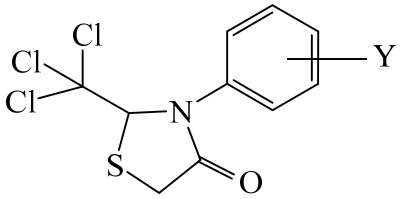
1. Introduction

1,3-thiazolidin-4-ones, also known as thiazolidin-4-ones, are known to have a very wide range of biological activity (Tripathi, Gupta, Fatima, Sonar, Verma, & Saraf, 2014)(Havrylyuk, Zimenkovsky, Vasylenko, Day, Smee, Grellier, & Lesyk, 2013)(Jain, Vaidya, Ravichandran, Kashaw, & Agrawal, 2012)(Abhinit, Ghodke & Pratima, 2009)(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). These compounds have been shown to possess anticancer, antiviral, anticonvulsant, antidiabetic, antimicrobial, antituberculosis, antihyperlipidemic, and cardiovascular activities. The importance of studying the spectroscopic and biological properties of substituted 2,3- diphenyl-1,3- thiazolidin-4-one systems (Figure 1) has been extensively documented (Woolston, Lee, Swinbourne, & Thomas, 1992; Woolston, Lee, & Swinbourne, 1993; Tierney *et al*., 1996; Tierney *et al*. 2005; Tierney, Koyfmann, Cannon, Mascavage, & Lagalante, 2008; Silverberg, *et al*., 2013). A wide array of thiazolidinones related to those shown in Figures 1-5 have been synthesized and analyzed by ^{13}C NMR. In all these examples the ^{13}C substituent chemical shift effects, particularly at C-2 in the thiazolidinone ring, have been documented in the literature (Woolston, *et al.,* 1992; Woolston, *et al.,* 1993; Tierney, *et al*., 1996; Tierney, *et al*, 2005; Tierney, *et al*., 2008; Silverberg, *et al*., 2013). Figure 1 represents a combination of substituents that potentially leads to a 13 x 13 matrix array of 169 compounds. Including this present study, 81 of the total 169 compounds in this matrix have been analyzed. These thiazolidinones also include moieties such as a trichloromethyl group attached to the C-2 carbon (Figure 2), a benzyl group attached to the N-3 site (Figure 3), a 2-pyridyl group attached to the N-3 site (Figure 4) or a cyclohexyl group attached to the N-3 site (Figure 5).



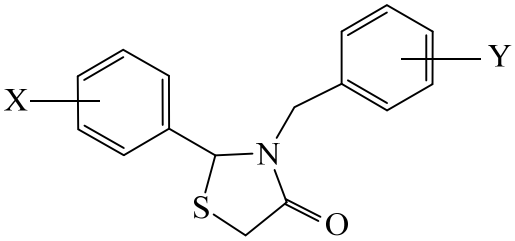
X = *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *p*-Br, *m*-Br, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *m*-OCH_3
Y = *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *p*-Br, *m*-Br, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *m*-OCH_3

Figure 1. These substituents can be mixed and matched in any combination to yield a 13 x 13 matrix of compounds.



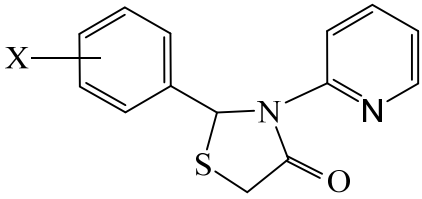
Y = *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *p*-Br, *m*-Br, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *m*-OCH_3

Figure 2.



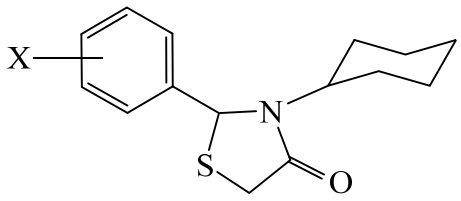
Either X = *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *p*-Br, *m*-Br, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *m*-OCH_3; Y = H
or Y = *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *p*-Br, *m*-Br, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *m*-OCH_3; X = H

Figure 3.



X = *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *p*-Br, *m*-Br, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *m*-OCH_3

Figure 4.



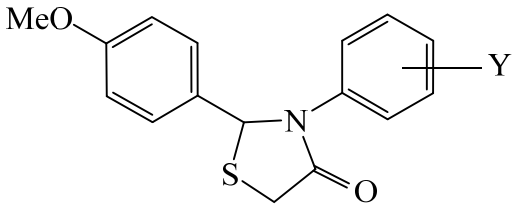
X = *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *p*-Br, *m*-Br, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *m*-OCH_3

Figure 5.

Utilizing substituent chemical shift data for ^{13}C chemical shifts at C-2 for the substituted 2-trichloromethyl-3-phenylthiazolidin-4-ones (Figure 2), these data showed the least sensitivity to Hammett correlations due to the presence of the overpowering trichloromethyl group attached to C-2. However, the application of a Swain Lupton dual substituent parameter approach did yield a good correlation for substituent effects from the phenyl group at N-3 (Issac, *et al.*, 1996). Hammett correlations for substituent chemical shift data for ^{13}C chemical shifts at C-2 for compounds shown in Figures 1, 3 and 4 do not show significant deviations, particularly for the *para*-methoxy compounds. Correlation issues associated with the para-methoxy group were first noticed in Hammett correlations of 3-cyclohexyl-2-substituted phenyl-1,3 thiazolidin-4-ones, Figure 5, (Cannon, *et al.*, 2013). The correlation deviation for the *para*-methoxy group was attributed to the slight pyramidalization of the N-3 atom in the thiazolidinone ring coupled with the ability of the cyclohexyl ring to flip from one chair conformation with the thiazolidinone ring equatorial to axial. The substituted *N*-benzyl compounds shown in Figure 3 do not exhibit pyramidalization at the N-3 nitrogen and are connected via the benzyl methylene to the planar benzyl aromatic ring which is almost orthogonal to the C-2 phenyl ring (Fun, Hemamalini, Shanmugavelan, Ponusswamy, & Jagatheesan, 2011). Substituents on both the C-2 phenyl and the *N*-benzyl rings (Figure 3) did produce measurable ^{13}C substituent chemical shift effects at the C-2 carbon and the *para*-methoxy group did not deviate from the correlations. Again, in these instances the opposing entity in the other ring was always hydrogen, and there were no dual substituent situations.

2. Results and Discussion

As already noted, ^{13}C substituent chemical shift effects at C-2 become problematic for the *para*-methoxy group when a cyclohexyl ring is attached to N-3 in the thiazolidinone ring. Shown in Table 1 are predicted and experimental ^{13}C chemical shift values at C-2, C-4 and C-5 for the disubstituted series of title compounds shown in Figure 6. The method for calculating the chemical shifts has been previously described (Tierney, *et al.*, 2005).



Y = *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *p*-Br, *m*-Br, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *m*-OCH_3

Figure 6.

Table 1. Experimental and calculated (in parenthesis) ^{13}C chemical shift data for 2-(4-methoxyphenyl)-3-(substituted phenyl)-thiazolidin-4-ones (Figure 6) in ppm relative to TMS.

compound	Substituent Y	C(2)	C(4)	C(5)
6a	*p*-NO_2	64.46 (64.33)	171.16 (170.70)	33.77 (33.31)
6b	*m*-NO_2	64.72 (64.74)	171.04 (170.13)	33.49 (33.29)
6c	*p*-F	65.45 (65.39)	170.97 (171.01)	33.37 (33.17)
6d	*m*-F	65.06 (65.13)	170.95 (171.00)	33.48 (33.32)
6e	*p*-Cl	65.06 (65.11)	170.86 (170.93)	33.41 (33.29)
6f	*m*-Cl	65.07 (65.14)	170.96 (171.01)	33.46 (33. 29)
6g	*p*-Br	64.90 (65.04)	170.77 (170.91)	33.39 (33.29)
6h	*m*-Br	65.11 (65.96)	170.97 (170.81)	33.48 (33.18)
6i	H	65.28 (65.91)	170.86 (171.10)	33.49 (33.36)
6j	*p*-CH_3	65.45 (65.48)	170.98 (171.01)	33.51 (33.35)
6k	*m*-CH_3	65.44 (65.48)	170.95 (170.96)	33.24 (33.34)
6l	*p*-OCH_3	65.44 (65.71)	170.82 (171.13)	33.24 (33.30)
6m	*m*-OCH_3	65.40 (66.09)	170.86 (171.73)	33.48 (34.08)

A Hammett correlation plot for the substituents' experimental chemical shifts for C-2 is shown in Figure 8. There is a clustering of substituents along the trend line instead of the normal linearity previously observed in other similarly substituted systems (Woolston, *et al.,* 1993). Even when there are a few reported aberrations, overall linearity is still present in the correlation (Cannon, *et al.*, 2013). Another indicator of the degree of scatter is discernible from a plot of the actual chemical shifts *versus* the calculated values shown for the series of compounds in Figure 9 (Tierney, *et al.*, 2005). Prior Hammett correlations for disubstituted systems were in concert with plots for predicted chemical shifts (Silverberg, *et al.*, 2013; Tierney, *et al.*, 2005). The first inkling that the *para*-methoxy group interfered with the transmission of substituent effects was in the instance where the *para*-methoxy group was fixed in the N-3 phenyl ring and the substituents were varied in the C-2 phenyl ring (Figure 1) (Tierney, *et al.*, 2008). In this instance where the *para*-methoxy group was fixed at N-3 the correlations were improved when a Swain-Lupton dual substituent parameter approach was taken. This, however, is not the case with the current set compounds. The Swain-Lupton approach allows for a more flexible assignment of the resonance and field effects from substituent to site, but the *para*-methoxy group's proximity to the C-2 site in the current set has an overpowering effect on the C-2 ^{13}C chemical shifts from substituents located on the more distant N-3 phenyl ring. This overpowering effect had previously been noted by Johnson in other interactions involving the presence of the *para*-methoxy group due to increased electron demand (Johnson, 1978).

Plot of Hammett σ *vs* ^{13}C Substituent Chemical Shift Values for C-2

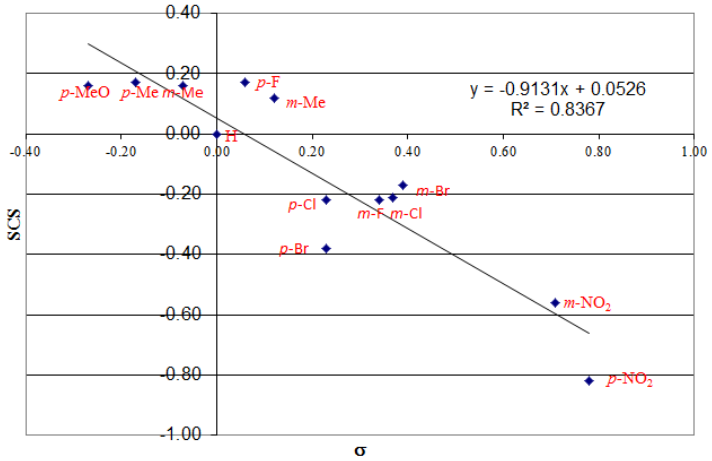


Figure 8. Plot of versus SCS for compounds shown in Figure 6.

^{13}C Chemical Shift Values for C-2 in a Series of N-3-phenyl substituted 2-(*p*-methoxyphenyl-3-phenyl-1,3-thiazolidin-4-ones

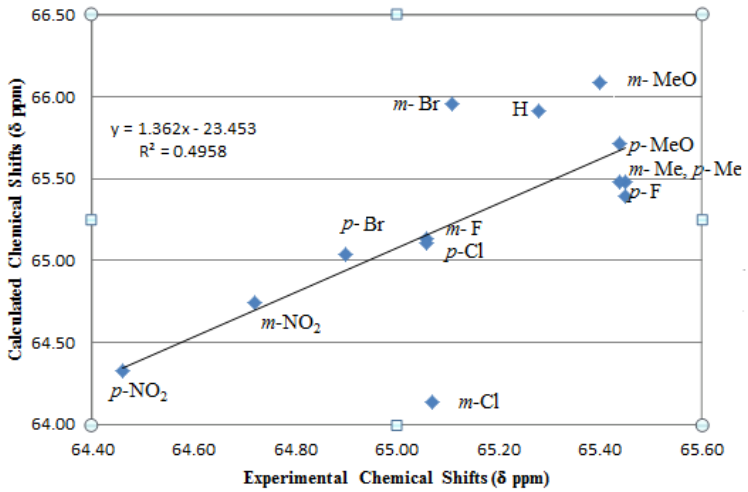


Figure 9. Plot of experimental versus calculated chemical shifts for compounds shown in Figure 6.

3. Conclusion

Two series of disubstituted diphenyl-1,3-thiazolidine-4-ones have been synthesized having the *para*-methoxy group as the set substituent in either the C-2 or N-3 aromatic ring, while the substituents have been varied in the other aromatic ring. By varying the substituent in one ring the effects on the ^{13}C chemical shift sensitivity at C-2 in the thiazolidinone ring can be used to determine the preferred charge build up at the C-2 carbon. As shown in previous investigations, the absence of a fixed *para*-methoxy group yields relatively good linear Hammett correlations and the charge build up is easy to assign. The two fixed *para*-methoxy-substituted series of compounds (Figure 6, and the counterpart with the methoxy group in the N-3 phenyl ring) do not conform to these Hammett trends. The presence of the *para*-methoxy group appears to cause an electronic effect that overpowers the ^{13}C signal at C-2 (as well as C-4 and C-5) in the thiazolidinone ring and does not work in concert with the other substituents. Interestingly, the presence of the *para*-methoxy group on the C-2 phenyl and a cyclohexane ring on N-3 also appears to perturb the ^{13}C signal at C-2, yet this is not the case if the moiety at N-3 is a benzyl ring. The *para*-methoxy group appears to work destructively with other substituents because of the highly electronegative oxygen and the presence of electron lone pairs that can back donate into the benzene ring.

4. Experimental

The thiazolidine-4-ones were prepared using the procedure previously described (2) by adapting a method originally utilized by Surrey (Surrey, 1967). Melting points are uncorrected; a Mel-Temp apparatus was used. All spectra were recorded on a Bruker Avance 400 at 298K observing ^{1}H and ^{13}C at 300.15 and 75.48 MHz, respectively. All samples were dissolved in $CDCl_3$ at concentrations of 100 mg/mL using precision bore 5 mm NMR tubes supplied by Norell, Inc.

^{1}H spectra were collected into 32K data sets over a spectral width of 3012.0 Hz using a 30° pulse; pulse width, 3.0 μs; acquisition time, 2.72 s; relaxation delay, 1.0 s; number of scans, 16. ^{13}C spectra were collected into 16K data sets over a spectral width of ±10.000 Hz with a 60° observed pulse using Waltz-16 decoupling; pulse width, 6.0 μs; acquisition time 409.6 ms; relaxation delay, 2.00 s; number of scans, 512. The spectrometer was locked to the deuterium resonance of the solvent ($CDCl_3$) and all chemical shifts were referenced to internal TMS (δ = 0.00 ppm). 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. 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 yields. Hammett and Swain-Lupton correlations were obtained using Excel in Microsoft Office.

2-(4-methoxyphenyl)-3-(4-nitrophenyl)-1,3-thiazolidin-4-one (**5a**) (44%); oil; υ cm^{-1} 1695 (C=O); ^{1}H NMR ($CDCl_3$): 8.20-6.80 (8H, m, aromatics), 6.21 (1H, s, CH), 3.95, 3.86 (2H, dd, CH_2, J=16.0 Hz), 3.66 (3 H, s, OCH_3); ^{13}C NMR: 171.16 (C4), 159.09 (Ar), 148.46 (Ar), 147.24 (Ar), 129.88 (Ar), 128.43 (Ar), 127.52 (Ar), 124.55 (Ar), 115.10 (Ar), 64.46 (C2), 55.69 (OMe), 33.77 (C5); (m/z) 330 (M^+, 20%), $C_{16}H_{14}O_4N_2S$ (330.36).

2-(4-methoxyphenyl)-3-(3-nitrophenyl)-1,3-thiazolidin-4-one (**5b**) (63 %); m.p. 67-8°C; υ cm^{-1} 1684 (C=O); ^{1}H NMR ($CDCl_3$): 8.06-6.77 (8H, m, aromatics), 6.17 (1H, s, CH), 3.95 (1H, dd, CH_2, J = 1.5 Hz and J = 16.2 Hz), 3.87 (1H, dd, CH_2, J = 0.8 Hz and J = 16.1 Hz), 3.72 (3 H, s, OCH_3);^{13}C NMR: 171.04 (C4), 160.16(Ar), 148.28 (Ar), 138.60(Ar), 131.38 (Ar), 131.15 (Ar), 129.66 (Ar), 128.45(Ar), 121.31 (Ar), 120.00 (Ar), 114.44 (Ar), 64.72 (C2), 55.22 (OMe), 33.49 (C5); (m/z) 330 (M^+, 100%), $C_{16}H_{14}O_4N_2S$ (330.36).

3-(4-fluorophenyl)-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**5c**) (44 %); oil; υ cm^{-1} 1695 (C=O); ^{1}H NMR ($CDCl_3$): 7.20-6.77 (8H, m, aromatics), 5.97 (1H, s, CH), 3.94 (1H, dd, CH_2, J = 1.7 Hz and J = 16.0 Hz), 3.85 (1H, d, CH_2, J = 15.9 Hz), 3.73 (3 H, s, OCH_3); ^{13}C NMR: 170.97 (C4), 162.32 (Ar), 159.93 (Ar, d, J = 12.3 Hz), 133.32 (Ar, d, J = 3.0 Hz), 130.64 (Ar), 128.59 (Ar), 127.88 (Ar, d, J = 8.8 Hz), 116.00 (Ar, d, J = 23.2), 114.14 (Ar), 65.45 (C2), 55.19 (OMe), 33.37 (C5); (m/z) 303 (M^+, 45%), $C_{16}H_{14}O_2NSF$ (303.36).

3-(3-fluorophenyl)-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**5d**) (48%); m.p. 87-9 °C; υ cm^{-1} 1688 (C=O); ^{1}H NMR ($CDCl_3$): 7.26-6.79 (8H, m, aromatics), 6.06 (1H, s, CH), 3.94 (1H, dd, CH_2, J = 1.5 Hz and J = 15.9 Hz), 3.84 (1H, dd, CH_2, J = 0.7 Hz and J = 15.9 Hz), 3.75 (3 H, s, OCH_3); ^{13}C NMR: 170.95 (C4), 163.82 (Ar), 161.36 (Ar), 159.99 (Ar), 138.99 (Ar, d, J = 9.6 Hz), 130.64 (Ar), 130.05 (Ar, d, J = 8.7 Hz), 128.28 (Ar), 120.92 (Ar, d, J =3.1 Hz), 114.28 (Ar), 113.41 (Ar, dd, J = 22.4 Hz and J = 92.5 Hz), 65.06 (C2), 55.23 (OMe), 33.48 (C5); (m/z) 303 (M^+, 29%), $C_{16}H_{14}O_2NSF$ (303.36).

3-(4-chlorophenyl)-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**5e**) (64%); m.p. 147-8 °C; υ cm^{-1} 1686 (C=O); ^{1}H NMR ($CDCl_3$): 7.22-6.77 (8H, m, aromatics), 6.02 (1H, s, CH), 3.92 (1H, dd, CH_2, J = 1.5 Hz and J = 15.9 Hz), 3.83 (1H, d, CH_2, J = 15.6 Hz), 3.73 (3 H, s, OCH_3); ^{13}C NMR: 170.86 (C4), 159.95 (Ar), 135.93 (Ar), 132.48 (Ar), 130.48 (Ar), 129.14 (Ar), 128.43 (Ar), 126.92 (Ar), 114.18 (Ar), 65.06 (C2), 55.16 (OMe), 33.41 (C5); (m/z) 319 (M^+, 100%), $C_{16}H_{14}O_2NSCl$ (319.81).

3-(3-chlorophenyl)-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**5f**) (49%); m.p. 117-8 °C; υ cm^{-1} 1687 (C=O); ^{1}H NMR ($CDCl_3$): 7.37-6.77 (8H, m, aromatics), 6.04 (1H, s, CH), 3.93 (1H, dd, CH_2, J = 1.0 Hz and J = 15.9 Hz), 3.83 (1H, d, CH_2, J = 15.9 Hz), 3.74 (3 H, s, OCH_3); ^{13}C NMR: 170.96 (C4), 160.02 (Ar), 138.62 (Ar), 134.52 (Ar), 130.49 (Ar), 129.89 (Ar), 128.38 (Ar), 127.13(Ar), 125.81 (Ar), 123.69 (Ar), 114.29 (Ar), 65.07 (C2), 55.23 (OMe), 33.46 (C5); (m/z) 319 (M^+, 22%), $C_{16}H_{14}O_2NSCl$ (319.81).

3-(4-bromophenyl)-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**5g**) (55%); m.p. 120-1 °C; IR: υ cm^{-1} 1686 (C=O); ^{1}H NMR ($CDCl_3$): 7.37-6.77 (8H, m, aromatics), 6.02 (1H, s, CH), 3.92 (1H, dd, CH_2, J = 1.6 Hz and J = 16.0 Hz), 3.82 (1H, dd, CH_2, J = 0.8 Hz and J = 16.0 Hz), 3.72 (3 H, s, OCH_3);^{13}C NMR: 170.77 (C4), 159.88 (Ar), 136,42 (Ar), 132.03 (Ar), 130.41(Ar), 128.35 (Ar), 127.15 (Ar), 120.39 (Ar), 114.15 (Ar), 64.90 (C2), 55.13 (OMe), 33.39 (C5); (m/z) 364 (M^+, 100%), $C_{16}H_{14}O_2NSBr$ (364.26).

3-(3-bromophenyl)-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**5h**) (67%); m.p. 115-16 ^{o}C; υ cm^{-1} 1688 (C=O); ^{1}H NMR ($CDCl_3$): 7.36-6.78 (8H, m, aromatics), 6.03 (1H, s, CH), 3.93 (1H, dd, CH_2, J = 1.4 Hz and J = 15.9 Hz), 3.83 (1H, d, CH_2, J = 15.9 Hz), 3.75 (3 H, s, OCH_3); ^{13}C NMR: 170.97 (C4), 160.06 (Ar), 138.72 (Ar), 130.50 (Ar), 130.19 (Ar), 130.08 (Ar), 128.70 (Ar), 128.42 (Ar), 124.25 (Ar), 122.44 (Ar), 114.32 (Ar), 65.11 (C2), 55.27 (OMe), 33.48 (C5); (m/z) 364 (M^+, 100%), $C_{16}H_{14}O_2NSBr$ (364.26).

2-(4-methoxyphenyl)-3-phenyl-1,3-thiazolidin-4-one (**5j**) (55%); m.p. 108-9 ^{o}C; υ cm^{-1} 1672 (C=O); ^{1}H NMR ($CDCl_3$): 7.31-6.80 (9H, m, aromatics), 5.99 (1H, s, CH), 3.92 (1H, dd, CH_2, J = 1.7 Hz and J = 15.8 Hz), 3.88 (1H, d, CH_2, J = 15.8 Hz), 3.76 (3 H, s, OCH_3).^{13}C NMR: 170.86 (C4), 159.81 (Ar), 137.43 (Ar), 131.04 (Ar), 128.98 (Ar), 128.40 (Ar), 126.99 (Ar), 125.79 (Ar), 114.07 (Ar), 65.28 (C2), 55.15 (OMe), 33.49 (C5); (m/z) 285 (M^+, 100%), $C_{16}H_{15}O_2NS$ (285.36).

2-(4-methoxyphenyl)-3-(4-methylphenyl)-1,3-thiazolidin-4-one (**5j**) (55%); m.p. 108-9 ^{o}C; υ cm^{-1} 1685 (C=O); ^{1}H NMR ($CDCl_3$): 7.21-6.77 (8H, m, aromatics), 5.99 (1H, s, CH), 3.95 (1H, dd, CH_2, J = 1.8 Hz and J = 16.0 Hz), 3.84 (1H, d, CH_2, J = 16.1 Hz), 3.74 (3 H, s, OCH_3)., 2.23 (3H, CH_3).^{13}C NMR: 170.98 (C4), 159.88 (Ar), 137.08 (Ar), 134.79 (Ar), 131.27 (Ar), 129.75 (Ar), 128.53 (Ar), 125.89(Ar), 114.10 (Ar), 65.45 (C2), 55.22 (OMe), 33.51 (C5), 21.00 (Me); (m/z) 299 (M^+, 40%), $C_{17}H_{17}O_2NS$ (299.39).

2-(4-methoxyphenyl)-3-(3-methylphenyl)-1,3-thiazolidin-4-one (**5k**) (60%); m.p. 239-40 ^{o}C; υ cm^{-1} 1684 (C=O); ^{1}H NMR ($CDCl_3$): 7.22-6.76 (8H, m, aromatics), 6.02 (1H, br d, CH, J = 0.7 Hz), 3.95 (1H, dd, CH_2, J = 1.8 Hz and J = 15.7 Hz), 3.84 (1H, dd, CH_2, J = 0.8 Hz and J = 16.0 Hz), 3.73 (3 H, s, OCH_3), 2.24 (3H, CH_3). ^{13}C NMR: 170.95 (C4), 159.82 (Ar), 138.96 (Ar), 137.29 (Ar), 131.18 (Ar), 128.78 (Ar), 128.43 (Ar), 128.01 (Ar), 126.66 (Ar), 122.92 (Ar), 114.06 (Ar), 65.41 (C2), 55.18 (OMe), 33.51 (C5), 21.28 (Me); (m/z) 299 (M^+, 100%), $C_{17}H_{17}O_2NS$ (299.39).

2-(4-methoxyphenyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**4l**) (54%); m.p. 119-120 ^{o}C, (lit. m.p.119-120 ^{o}C) (1); υ cm^{-1} 1623 (C=O); ^{1}H NMR ($CDCl_3$): 7.20-6.74 (8H, m, aromatics), 5.94 (1H, s, CH), 3.93 (1H, dd, CH_2, J = 1.6 Hz and J = 15.7 Hz), 3.88 (1H, d, CH_2, J = 15.6 Hz), 3.70 (3H, s, OCH_3), 3.67 (3 H, s, OCH_3). ^{13}C NMR: 170.82 (C4), 159.73 (Ar), 158.20 (Ar), 131.05 (Ar), 129.91 (Ar), 128.52 (Ar), 127.44 (Ar), 114.20 (Ar), 113.91 (Ar), 65.44 (C2), 55.10 (OMe), 55.03 (OMe), 33.24 (C5); (m/z) 315 (M^+, 100%), $C_{17}H_{17}O_3NS$ (315.39).

2-(3-methoxyphenyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**5m**) (59%); m.p. 192-3 ^{o}C; υ cm^{-1} 1683 (C=O); ^{1}H NMR ($CDCl_3$): 7.22-6.70 (8H, m, aromatics), 6.02 (1H, s, CH), 3.94 (1H, dd, CH_2, J = 1.5 Hz and J = 15.7 Hz), 3.83 (1H, d, CH_2, J = 15.6 Hz), 3.73 (3H, s, OCH_3), 3.68 (3 H, s, OCH_3). ^{13}C NMR: 170.86 (C4), 159.97 (Ar), 138.67 (Ar), 131.28 (Ar), 129.61 (Ar), 128.40 (Ar), 117.98 (Ar), 114.19 (Ar), 112.75 (Ar), 111.89 (Ar), 65.40 (C2), 55.23 (MeO), 55.22 (MeO), 33.48 (C5); (m/z) 315 (M^+, 100%), $C_{17}H_{17}O_3NS$ (315.39).

Acknowledgements

We would like to thank Dr. David Dalton, Dr. Charles DeBrosse, and the Chemistry Department of Temple University for allowing us to run the NMR spectra on their Bruker 400 spectrometer. In addition, this work was funded in part by Pennsylvania State University Schreyer Honors College. Part of the work described here was taken from Chino Mannikarottu's honor's thesis in the Shreyer Honors College.

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. M., Tierney, J., Kistler, K., Yennawar, H., & Lagalante, A. (2013). An Experimental and Theoretical Conformational Study of a Series of Substituted 3-cyclohexyl-2-phenyl-1,3-thiazolidin-4-ones. *Intl. J. Chem*., *5*(3), 46-56. http://dx.doi.org/10.5539/ijc.v5n3p46

Fun, H. K., Hemamalini, M., Shanmugavelan, P., Ponuswamy, A., & Jagatheesan, R. (2011). 3-Benzyl 2-phenyl-1,3-thiazolidin-4-one. *Acta Crystallogr. Sect E*, *67*(Pt 10), o2706. http://dx.doi.org/10.1107/S1600536811037706

Havrylyuk, D., Zimenkovsky, B., Vasylenko, O., Day, C. W., Smee, D. F., Grellier, P., & Lesyk, R. (2013). Synthesis and biological activity evaluation of 5-pyrazoline substituted 4-thiazolidinones. *Eur. J. Med. Chem.*, *72*, 52-77. http://dx.doi.org/10.1016/j.ejmech.2013.05.044

Issac, R., Tierney, J., Mascavage, L., McCoy, M., Findeisen, A., & Kilburn, J. (1996). Synthesis, spectroscopic and structural properties of novel substituted 2-trichloromethyl-3-phenyl-1,3-thiazolidin-4-ones. *Heterocyclic Communications, 2*, 227-232. http://dx.doi.org/10.1515/HC.1996.2.3.227

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://dxdoi.org/10.1016/j.bmc.2012.03.069

Johnson, C. D. (1978). Use of the tool of increasing electron demand in determination of the status of the Yukawa-Tsuno (YT) Equation. *Journal of Organic Chemistry, 43,* 1814-1815. http://dx.doi.org/10.1021/jo00403a043

McGarity, D., Tierney, J., & Lagalante, A. (2014). An Anomalous Hammett Correlation for a Series of Substituted 3-Benzyl-2-phenyl-1,3-thiazolidin-4-ones. *Intl. J. Chem*., *6*(4), 12-18. http://dx.doi.org/10.5539/ijc.v6n4p12

Silverberg, L. J., Bear, E. R., Foose, K. N., Kirkland, K. A., McElvaney, R. R., Cannon, K., & 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*(4), 120-127. http://dx.doi.org/10.5539/ijc.v5n4p120

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

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., & Kilburn, J. (1996). Effects and conformational analysis of some substituted 2,3-diphenyl-1,3-thiazolidin-4-ones. *Magnetic Resonance in Chemistry, 34*, 573-576. http://dx.doi.org/10.1002/(SICI)1097-458X(199608)34:8<573::AID-OMR928>3.0.CO;2-D

Tierney, J., Sheridan, D., Kovalesky, K., Mascavage, L. M., Schneider, K., & Sheely, C. (2000). Substituent effects for some substituted 3-benzyl-2-phenyl-1,3-thiazolidin-4-ones using ^{1}H and ^{13}C NMR. *Heterocyclic Communications, 6*, 105-111. http://dx.doi.org/10.1515/HC.2000.6.2.105

Tierney, J., Mascavage, L. M., Sheridan, D., Gorbecheva, D., Ripp, M., & Son, S. (2005). A preliminary study on predicting the ^{13}C chemical shifts for a series of disubstituted 2,3-diphenyl-1,3-thiazolidin-4-ones. *Heterocyclic Communications, 11*, 215-222. http://dx.doi.org/10.1515/HC.2005.11.3-4.215

Tierney, J., Colasante, N., Eagles, J., Kelly, S., Lehmicke, G., Lucas, O., & Lagalante, A. F. (2007). A Comparison Of Substituent Effects Using ^{13}C Chemcial Shifts for A Series of Substituted 2-Phenyl-3-pyridyl-1,3-thiazolidin-4-ones Compared To Similarly Substituted 1,3-thiazolidin-4-ones. *Heterocyclic Comm., 13*, 335-342. http://dx.doi.org/10.1515/HC.2007.13.6.335

Tierney, J., Koyfmann, V., Cannon, K., Mascavage, L. M., & Lagalante, A. (2008). A second study–predicting the ^{13}C chemical shifts for a series of substituted-3-(4-methoxy-phenyl)-2-phenyl-1,3-thiazolidin-4-ones. *Heterocyclic Communications, 14*, 453-460. http://dx.doi.org/10.1515/HC.2008.14.6.453

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

Woolston, C. R. J., Lee, J. B., Swinbourne, F. J., & Thomas, W. A. (1992). Proton NMR investigation of some substituted 1,3-thiazolidin-4-ones. *Magnetic Resonance in Chemistry, 30*, 1075-1078. http://dx.doi.org/10.1002/mrc.1260301109

Woolston, C. R. J., Lee, J. B., & Swinbourne, F. J. (1993). Carbon-13 NMR investigation of some substituted 1,3-thiazolidin-4-ones. *Magnetic Resonance in Chemistry, 31*, 348-351. http://dx.doi.org/10.1002/mrc.1260310407