

Synthesis and spectroscopic properties of a series of novel 2-aryl-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-ones

Lee J. Silverberg,^{*a} Carlos Pacheco,^b Anthony Lagalante,^c John Tierney,^d Joshua T. Bachert,^a J. Austin Bayliff,^a Ryan V. Bendinsky,^a Aaron S. Cali,^a Liuxi Chen,^a Avril D. Cooper,^a Michael J. Minehan,^a Caitlin R. Mroz,^a Duncan J. Noble,^a Alexander K. Weisbeck,^a Yiwen Xie,^a and Ziwei Yang^a

^a Pennsylvania State University, Schuylkill Campus, 200 University Drive, Schuylkill Haven, PA, USA 17972

^b Pennsylvania State University, University Park Campus, 104 Chemistry Building, Room 14, University Park, PA, USA 16802

^c Villanova University, Department of Chemistry, Mendel Science Center, 800 Lancaster Avenue, Villanova, PA, USA 19085

^d Pennsylvania State University, Brandywine Campus, 25 Yearsley Mill Road, Media, PA, USA 19063

E-mail: ljs43@psu.edu

DOI: <https://doi.org/10.24820/ark.5550190.p009.875>

Abstract

A series of thirteen novel 2-aryl-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-ones was prepared at room temperature by T3P-mediated cyclization of *N*-phenyl-*C*-aryl imines with thiosalicylic acid. The spectroscopic and physical properties are reported and discussed. ¹H-¹⁹F and ¹³C-¹⁹F couplings were observed in the NMR spectra of fluorinated compounds. Through-space interactions were observed in the ¹H and ¹³C NMR spectra of the *ortho*-nitro compound. Trends were observed in the IR and UV absorptions of the *ortho/meta/para*-nitro series.

Keywords: Benzothiazinone, T3P, fluorine, imine, spectroscopy

Introduction

Compounds with a 2,3-dihydro-4H-1,3-benzothiazin-4-one scaffold (Figure 1) have shown a wide range of bioactivity, including HIV-RT inhibitory,^{1,2} antitumor,³⁻⁵ antimicrobial,⁶ and antimalarial.⁷ More narrowly, *N*-aryl (R¹ = aryl or heteroaryl) compounds in this family have shown antitumor,^{3,5,8} cyclooxygenase COX-2 enzyme inhibition,⁹ HIV-RT inhibition,¹ and antimicrobial activity.¹⁰ Although this structure is not yet considered to be a privileged scaffold,

in 2010 Welsch, Snyder, and Stockwell identified 46 privileged scaffolds, of which a remarkable 23 contained a benzene ring fused to a heterocycle.¹¹

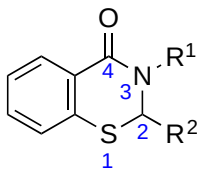


Figure 1. 2,3-Dihydro-4*H*-1,3-benzothiazin-4-one skeleton (R^1 = H, alkyl, aryl, heteroaryl, R^2 = alkyl, aryl, heteroaryl).

A variety of methods have been reported for the synthesis of 2,3-dihydro-4*H*-1,3-benzothiazin-4-ones.¹² The most commonly used method for preparation of these compounds is the condensation of an imine with thiosalicylic acid, which can be done by premaking the imine or by a three-component coupling of an amine, an aldehyde or ketone, and a thioacid. However, while compounds where R^1 is hydrogen or alkyl are readily prepared by this method, the *N*-aryl compounds are more difficult,¹³ due to the reduced nucleophilicity of the nitrogen. This may explain why the number of *N*-aryl and *N*-heteroaryl compounds that have been synthesized is relatively small (approximately 40 out of 500).^{1,5,8-10,13-25} Our initial investigations^{13,18} into the synthesis of 2,3-diphenyl-2,3-dihydro-4*H*-1,3-benzothiazin-4-one (**1j**) were unsuccessful using refluxing toluene, refluxing xylenes, and reaction using dicyclohexylcarbodiimide,¹³ as well as published methods for preparation of *N*-aryl-2,3-dihydro-4*H*-1,3-benzothiazin-4-ones, including $\text{Na}_2\text{SO}_4/1,4\text{-dioxane}$ ⁵ and *p*-toluenesulfonic acid/toluene/reflux.⁹ We succeeded using 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P) as a coupling agent.^{13,18} This method has now been applied to a full series of new 2-aryl-3-phenyl-2,3-dihydro-4*H*-1,3-benzothiazin-4-ones, the crystal structures of some of which we have previously reported.^{17-19,25} Herein, we report the synthesis and physical and spectroscopic properties of the full series.

Results and Discussion

Synthesis

Imines **2a-i** and **2k-n** for this study, all of which are known compounds, were prepared by heating aldehydes **3a-i** and **3k-n** with aniline **4** at reflux in toluene while removing water *via* a Dean-Stark trap. Imines **2a-d**, **2f-i**, **2k**, and **2m** were recrystallized. Imines **2e**, **2l**, and **2n** were liquids, which were used as obtained. No attempt was made to optimize yields. Imine **2j** is available commercially.

The condensation of thiosalicylic acid **5** with imines **2a-n** was performed as previously reported,^{13,17-19,25} using T3P as a promoter and pyridine as a base (Scheme 1). The reactions were

run at room temperature, whereas the similar method reported by Kitsiou was run at 90 °C.¹⁶

Yields were modest (Table 1), but no attempt was made to optimize yields, which were calculated from the imines **2a-n**, whether **2** was a recrystallized solid or crude liquid. Only one *N*-aryl example was reported by Kitsiou, and the yield of 53% was significantly lower than their yields for *N*-alkyl compounds,¹⁶ so it can again be seen that *N*-aryl compounds in this family are more difficult in general to prepare than *N*-alkyl compounds, and the yields reported here are partly a function of that. What is most notable about the syntheses reported here is that the reaction succeeded with every *C*-aryl substituent attempted, including both electron-withdrawing and electron-donating, and in either *ortho*, *meta* or *para* positions. Fourteen compounds are reported herein. The synthesis and X-ray crystallographic structures of compounds **1a-c** and **1j** have been previously reported.^{13,17-19} Preparation of compound **1b** was repeated and the revised yield is reported here. Yields and spectroscopic data are compiled in Table 1, with only key signals common to each product compared. Spectroscopic data has only been previously reported for **1j**,¹³ which is included in Table 1, along with a remeasurement of the ultraviolet-visible (UV-Vis) spectrum, for comparison. Full spectral data and physical properties are provided in the Experimental Section.

¹H NMR Spectroscopy

The signals from the C2 proton of compounds **1a-n** corresponding to each of the substituted 2-aryl moieties are compared in Figure 2. The signal for the *ortho*-nitro compound **1a** was at 7.01 ppm, but the others (all *meta*- or *para*-substituted) ranged only from 6.01 to 6.14 ppm. This is similar to the ranges observed by Tierney²⁶ and Woolston²⁷ for *meta*- and *para*-substituted 2-aryl-3-phenyl-1,3-thiazolidin-4-ones (five-membered heterocycles).

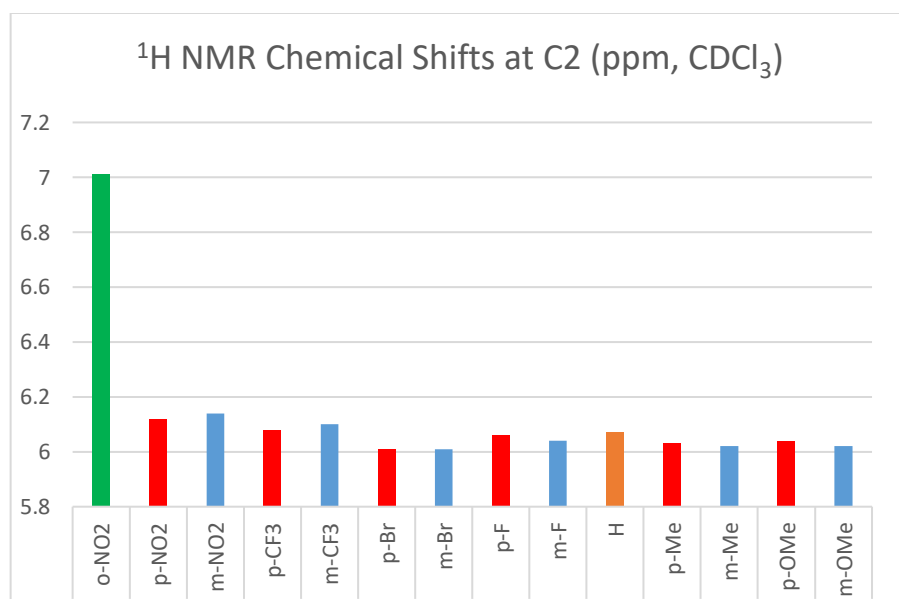
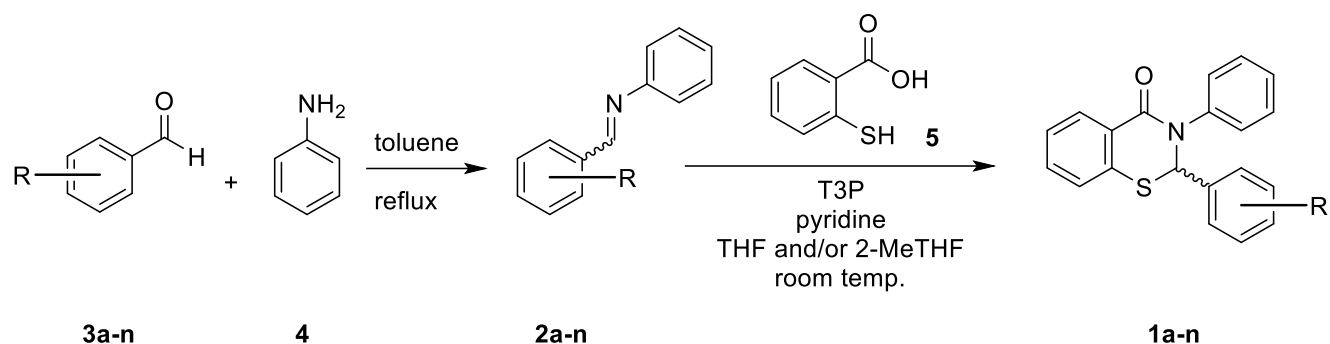


Figure 2. ¹H chemical shifts at C2 (ppm, CDCl₃) (2-aryl moiety substitution: orange = unsubstituted, red = *para*-substituted, blue = *meta*-substituted, green = *ortho*-substituted).



Scheme 1. Preparation of 2-aryl-3-phenyl-2,3-dihydro-4*H*-1,3-benzothiazin-4-ones.

Table 1. 2-Aryl-3-phenyl-2,3-dihydro-4*H*-1,3-benzothiazin-4-ones **1** prepared and comparison of key spectroscopic signals

Compound	R	Yield of 1 from 2 (%)	¹ H NMR Chemical Shifts at C2 (ppm, CDCl ₃)	¹³ C NMR Chemical Shifts at C2 (ppm, CDCl ₃)	¹³ C NMR Chemical Shifts at C4 (ppm, CDCl ₃)	IR Absorbance of Carbonyl (C4) (cm ⁻¹)	UV/Vis λ _{max} and approx. λ _{max} of shoulder peak (CH ₃ CN) (nm)
1a ¹⁹	<i>o</i> -NO ₂	14 ^a	7.01	61.0	164.3	1658	275, 326
1b ¹⁹	<i>p</i> -NO ₂	30 ^b	6.12	64.6	163.4	1652	287, 326
1c ¹⁷	<i>m</i> -NO ₂	40 ^b	6.14	64.6	163.4	1654	281, 317
1d	<i>p</i> -CF ₃	38 ^b	6.08	64.8	163.6	1651	278, 314
1e	<i>m</i> -CF ₃	12 ^{c,e}	6.10	64.9	163.6	1649	275, 314
1f	<i>p</i> -Br	35 ^b	6.01	64.8	163.6	1646	275, 314
1g	<i>m</i> -Br	23 ^b	6.01	64.6	163.6	1652	278, 317
1h	<i>p</i> -F	15 ^b	6.06	64.8	163.7	1648	272, 314
1i	<i>m</i> -F	43 ^b	6.04	64.8	163.6	1647	275, 314
1j ^{13,18}	H	35 ^b	6.07 ¹³	65.3 ¹³	163.8 ¹³	1682 ¹³	275, 314
1k	<i>p</i> -Me	30 ^d	6.03	65.1	163.8	1646	278, 314
1l	<i>m</i> -Me	16 ^{a,e}	6.02	65.2	163.8	1648	278, 314
1m	<i>p</i> -OMe	32 ^a	6.04	65.0	163.8	1645	284, 314
1n	<i>m</i> -OMe	40 ^{a,e}	6.02	65.2	163.8	1653	278, 314

^aIsolated by chromatography and then two recrystallizations. ^bIsolated by chromatography and then recrystallization. ^cIsolated by chromatography, then trituration with hexanes, and then recrystallization. ^dIsolated by hot filtration in EtOH and then recrystallization from toluene/hexanes. ^eThe imine **2** was used as a crude liquid.

Hammett correlation attempts

Attempts were made to correlate ^1H and ^{13}C substituent chemical shifts with Hammett σ constants. There were some general trends that could be discerned for both electron-withdrawing and electron-donating groups on the C-2 aryl, but they were not robust correlations. The same was true when UV λ_{max} values were plotted against Hammett σ constants. It is believed that the more complex structure and competing electronic influences within the fused 2,3-diaryl-2,3-dihydro-4*H*-1,3-benzothiazin-4-ones is the reason for the absence of clear correlations as witnessed by Tierney²⁶ and Woolston²⁷ in the simpler 1,3-thiazolidin-4-one systems.

Nitro compounds

The C2 proton resonance in *o*-nitro compound **1a** was significantly more downfield than in the *m*- and *p*-nitro compounds **1b** and **1c**. This indicated a through-space interaction between the proton and a negatively charged oxygen in the nitro group. The previously reported X-ray crystal structure of **1a**¹⁹ (Figure 3) showed that in the solid state one of the nitro oxygens is near the hydrogen on C2, with an intramolecular distance of 2.404 Å between the H and the O. This is close enough that a C-H...O hydrogen bond may exist.²⁸

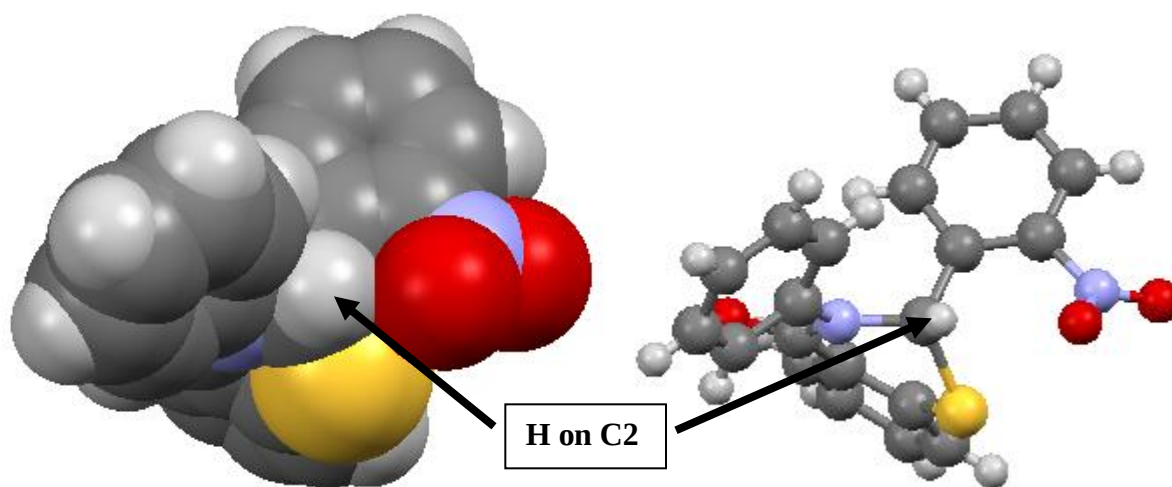


Figure 3. Space-filling and Ball and Stick drawings of the X-ray crystal structure of **1a**.¹⁹

Fluorinated compounds

Four of the compounds prepared have one or more fluorines. These are of interest for two reasons. One is the physical and biological properties that fluorine imparts to pharmaceuticals.^{29,30} The other is the potential to exploit ^1H - ^{19}F and ^{13}C - ^{19}F spin-spin coupling ($^nJ_{\text{HF}}$ and $^nJ_{\text{CF}}$) for ^1H and ^{13}C chemical shift assignments in NMR spectroscopy.³¹⁻³⁷

The *p*-fluoro compound **1h** showed a signal at 6.96 ppm for the two hydrogens *ortho* to the fluorine. The signal displayed a triplet pattern with ~ 8.3 Hz separation between the peaks. This separation is believed to stem from the $^3J_{\text{HH}}$ and $^3J_{\text{HF}}$ couplings of the *ortho* proton to the *meta* (with respect to F) and to the fluorine itself, respectively. The $^3J_{\text{HH}}$ and $^3J_{\text{HF}}$ couplings apparently overlap. Raising the temperature from room to 40 °C led to sharpening of the triplet, believed to be the result of faster equilibration between aryl ring-rotation conformers. The spectrum of the *m*-fluoro compound **1i** also showed an apparent triplet, with additional fine splitting, of one hydrogen at 6.95 ppm, which was assigned to the position which is *para* to the thiazine ring and *ortho* to the fluorine.

The spectra of trifluoromethyl compounds **1d** and **1e**, which have no hydrogens on adjacent carbons, did not show any noticeable extra splittings that would be due to ^1H - ^{19}F coupling.

^{13}C NMR Spectroscopy

There was very little variation in the C4 (C=O) signal (Figure 4). The range was only 163.4-164.3 ppm, and only 163.4-163.8 with the *o*-nitro excluded. The variance of 0.5 ppm for the *meta*- and *para*-substituted compounds is similar to that seen for 2-aryl-3-phenyl-1,3-thiazolidin-4-ones by Tierney²⁶ and Woolston.³⁸ Among the *meta*- and *para*-substituted compounds, the chemical shift values increased as electron withdrawing decreased and electron donation increased.

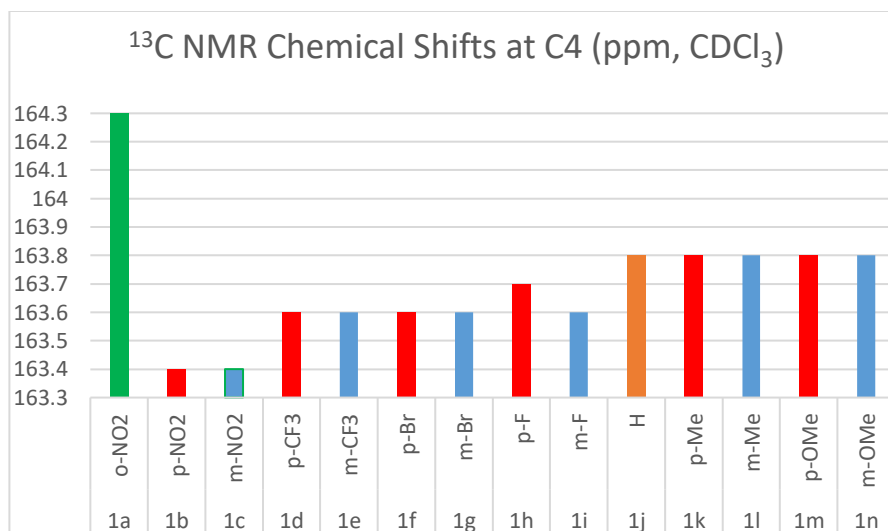


Figure 4. ^{13}C chemical shifts at C4 (ppm, CDCl_3) (2-aryl moiety substitution: orange = unsubstituted, red = *para*-substituted, blue = *meta*-substituted, green = *ortho*-substituted).

The signal for C2 (Figure 5) showed a range of only 64.6-65.3 ppm, except for *o*-nitro **1a**, which showed the signal at 61.0 ppm. The chemical shifts for the *meta*- and *para*-substituted compounds spanned a smaller variance (0.7 ppm) than that reported (~1.4-1.5 ppm) for 2-aryl-3-phenyl-1,3-thiazolidin-4-ones by Tierney²⁶ and Woolston.³⁸ Among the *meta*- and *para*-substituted compounds, the chemical shift values increased overall as electron withdrawing decreased and electron donation increased, but was not always consistent among two data points, e.g. the *m*-CF₃ compound **1d** had a higher value than the *m*-bromo compound **1g**.

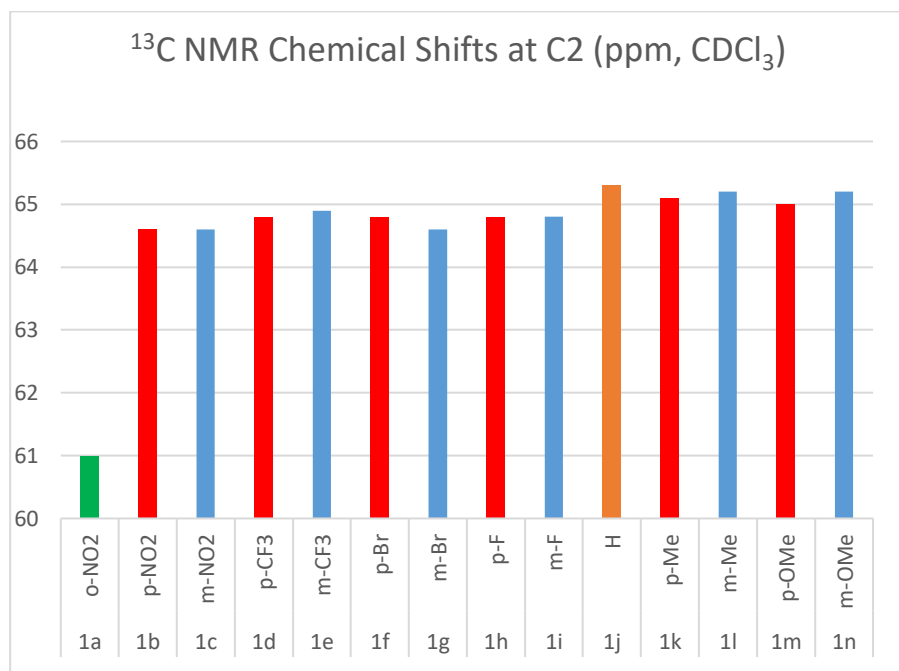


Figure 5. ¹³C chemical shifts at C2 (ppm, CDCl₃) (2-aryl moiety substitution: orange = unsubstituted, red = *para*-substituted, blue = *meta*-substituted, green = *ortho*-substituted).

Nitro compounds

In its ¹³C spectrum, the C2 carbon in the *o*-nitro compound **1a** was significantly more upfield, at 61.0 ppm, than in the other nitro compounds,. This indicated a through-space interaction between the carbon and the positively charged nitrogen in the *ortho* position. The X-ray crystal structure¹⁹ showed an intramolecular distance of 2.999 Å between C2 and the nitrogen in the solid state (Figure 6), close enough to indicate a non-bonded interaction.³⁹

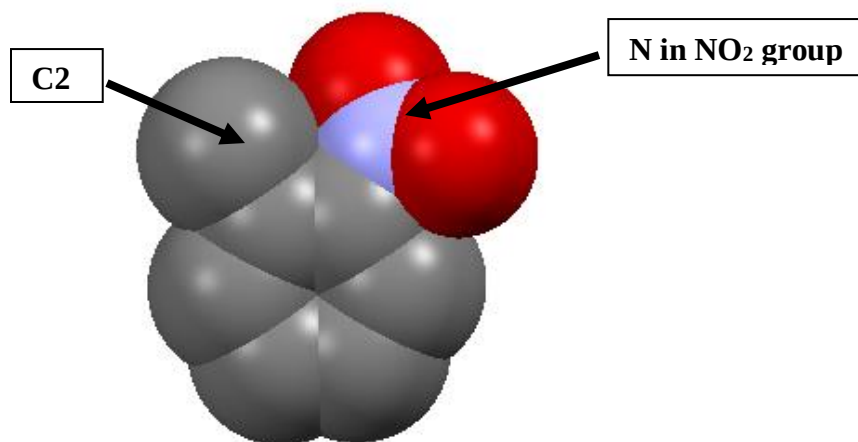


Figure 6. Partial space-filling drawing of the X-ray crystal structure of **1a** to allow visualization of C2 and the nitro group.¹⁹

Fluorinated compounds

The fluorinated compounds **1h**, **1i**, **1d**, and **1e** all displayed ^{13}C - ^{19}F coupling.

The *p*-fluoro compound **1h** showed four doublets attributable to the carbons that were *ipso*, *ortho* (2 carbons), *meta* (2 carbons), and *para* to the fluorine (Figure 7). The *m*-fluoro compound **1i** displayed seven doublets from C-F coupling – 1 *ipso*, 2 *ortho*, 2 *meta*, 1 *para*, and at C2 ($^4J_{\text{CF}} = 2$ Hz). The coupling constants for the aromatic carbons in all cases were close to the expected values of ~250 Hz for the *ipso* carbon ($^1J_{\text{CF}}$), ~20 Hz for the *ortho* carbons ($^2J_{\text{CF}}$), ~8 Hz for the *meta* carbons ($^3J_{\text{CF}}$) and ~3 Hz for the *para*-carbon ($^4J_{\text{CF}}$).³⁷

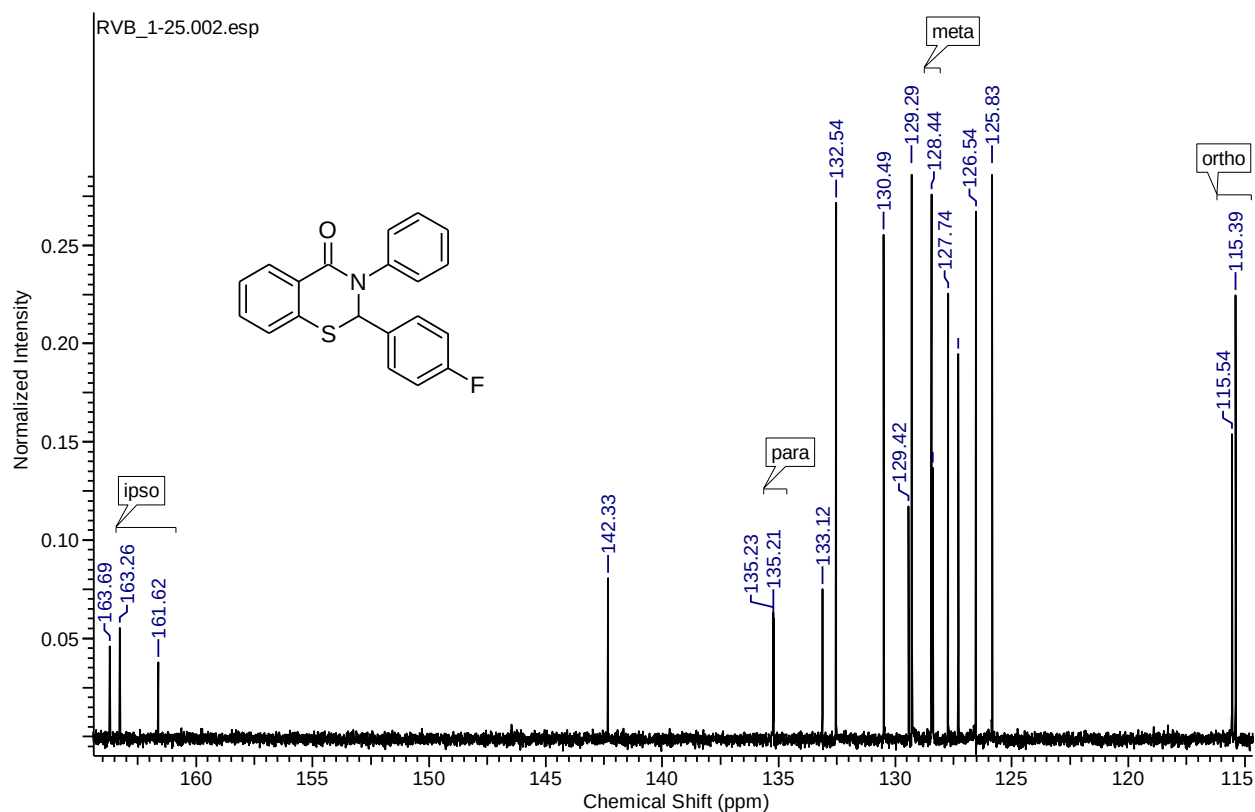


Figure 7. Aromatic ^{13}C - ^{19}F couplings in the ^{13}C NMR spectrum of *p*-fluoro compound **1h**.

Similarly, multiple quartets due to C-F splitting were observed in the spectra of the trifluoromethyl compounds **1d** and **1e**. In *m*-trifluoromethyl compound **1e**, four quartets were identified resulting from splitting by the three fluorines (Figure 8). These originated from the CF_3 carbon, the aromatic carbon connected to it, and the *ortho* carbons. The coupling constants were 272.7 Hz for $^1J_{\text{CF}}$, 32.7 Hz for $^2J_{\text{CF}}$, and between 3 and 4 Hz for $^3J_{\text{CF}}$, all as expected.³⁵ In the *p*-trifluoromethyl compound **1d** three C-F couplings were observed, also from the CF_3 carbon ($^1J_{\text{CF}}$ = 271.7 Hz), the aromatic carbon connected to it ($^2J_{\text{CF}}$ = 32.6 Jz), and one signal for the two *ortho* carbons ($^3J_{\text{CF}}$ = 3.7 Hz).

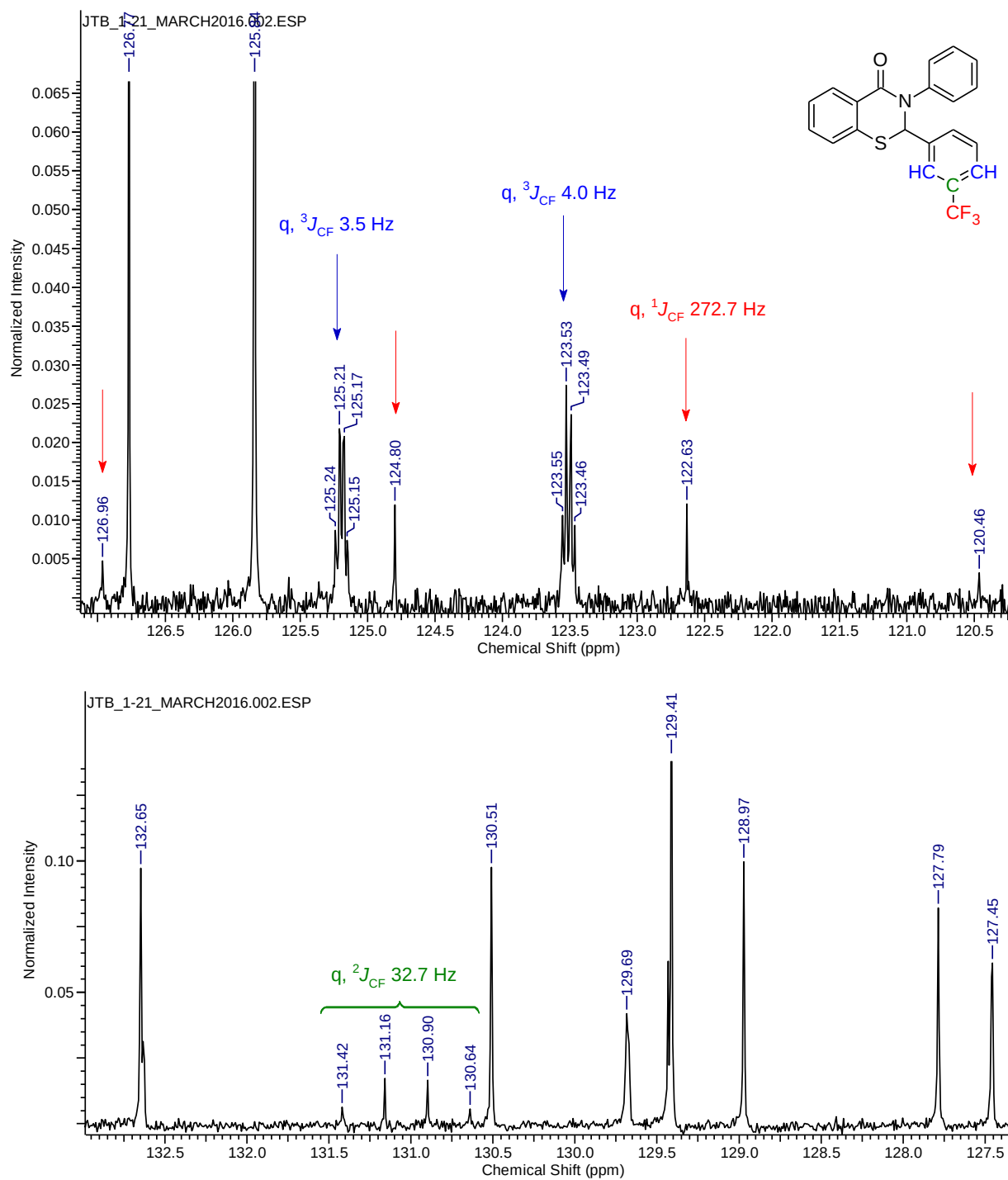


Figure 8. ^{13}C - ^{19}F splittings in the ^{13}C NMR spectrum of *m*- CF_3 compound **1e**.

IR Spectroscopy

In the infrared spectra, the substituted compounds **1b-1i** and **1k-1n** showed bands in a range of 1645-1658 cm^{-1} (Figure 9). Interestingly, the carbonyl (C4) in the unsubstituted compound **1j** showed absorption at a much higher wavenumber, 1682 cm^{-1} ,¹³ than for any of the substituted compounds. This analysis was repeated in case of error, but the result was very close, 1684 cm^{-1} . There was no discernible electronic pattern to the absorptions.

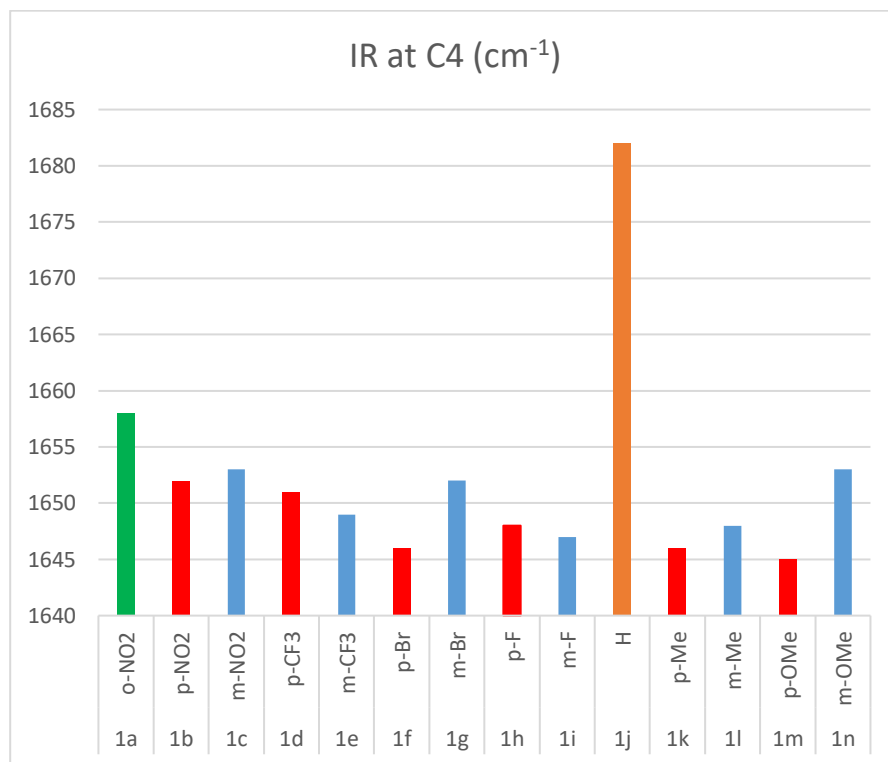


Figure 9. IR absorptions of the carbonyl (cm^{-1}) (2-aryl moiety substitution: orange = unsubstituted, red = *para*-substituted, blue = *meta*-substituted, green = *ortho*-substituted).

Nitro compounds

In the nitro series **1a-c**, the wavenumber increased slightly as the substituent moved closer to C2 (*para* 1652 cm^{-1} , *meta* 1654 cm^{-1} , *ortho* 1658 cm^{-1}).

UV-Vis Spectroscopy

All ultraviolet-visible spectra were run in acetonitrile. In each case, the λ_{max} peak showed a shoulder peak. The wavelength of the top of the side peak must be considered an estimate, since it was difficult to ascertain the wavelength of the crest of the peak. We had not previously noted the side peak when we recorded the spectrum of **1a** in cyclohexane.¹³ The spectrum of **1a** was recorded again in cyclohexane, and there was in fact a shoulder as in the spectrum in acetonitrile. The wavelengths of λ_{max} in CH_3CN ranged from 272-287 nm (Figure 10). There was no discernible

overall electronic pattern to the absorptions. The shoulders ranged from approximately 314-326 nm. The side peak was not present in 2,3-diphenyl-2,3,5,6-tetrahydro-4*H*-1,3-thiazin-4-one,¹³ so it is apparently due to the fused benzene ring.

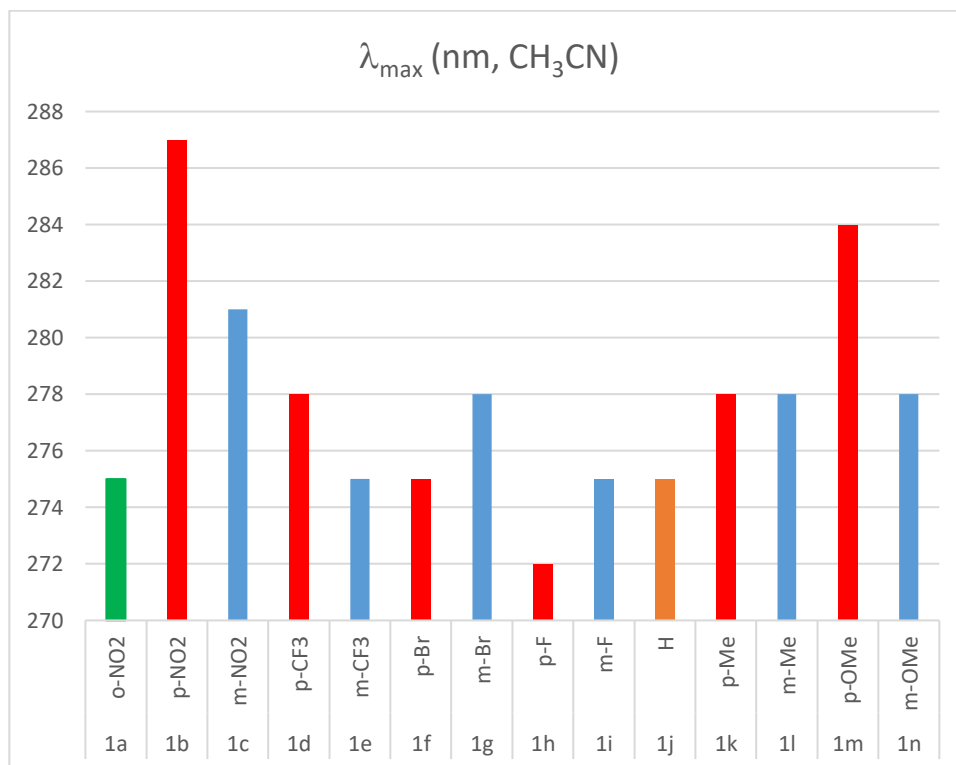


Figure 10. UV Absorptions at λ_{max} (nm) (2-aryl moiety substitution: orange = unsubstituted, red = *para*-substituted, blue = *meta*-substituted, green = *ortho*-substituted).

Nitro compounds

The nitro series **1a-c** showed increasing λ_{max} progressing from *ortho* to *meta* to *para*.

Conclusions

A series of novel 2-aryl-3-phenyl-2,3-dihydro-4*H*-1,3-benzothiazin-4-ones was synthesized at room temperature using T3P as a promoter. Among the *meta*- and *para*-substituted compounds there was little variation in ^1H and ^{13}C NMR signals at C2, and the same was true of the ^{13}C NMR and IR signals at C4. The carbonyl (C4) IR signal of **1j** (unsubstituted) was significantly different, however. As electron withdrawing decreased/electron donating increased, the chemical shifts of the ^{13}C NMR signals for C2 and C4 generally increased. The *o*-nitro compound **1a** displayed through-space interactions in the ^1H and ^{13}C NMR spectra, consistent with the X-ray structure. The fluorinated compounds **1f**, **1g**, **1d**, and **1e** displayed ^{13}C - ^{19}F couplings and **1h** and **1i** also showed ^1H - ^{19}F coupling. The UV spectra all showed two absorptions, the second being due to the fused benzene ring.

Investigation of the biological properties is in the early stages, while the syntheses of a second (3-aryl-2-phenyl) and third (2,3-diaryl) series of compounds are well underway.

Experimental Section

General. Toluene, tetrahydrofuran, 2-methyltetrahydrofuran, pyridine, aniline, thiosalicylic acid, 3-methoxybenzaldehyde, 4-bromobenzaldehyde, 3-bromobenzaldehyde, *m*-tolualdehyde, 3-fluorobenzaldehyde, 4-fluorobenzaldehyde, and 3-nitrobenzaldehyde, were purchased from Sigma-Aldrich (St. Louis, MO). 3-(Trifluoromethyl)benzaldehyde and 4-(trifluoromethyl)benzaldehyde were purchased from Matrix Scientific (Columbia, SC). 2-Nitrobenzaldehyde was purchased from Eastman Kodak Co. (Rochester, NY). *N*-Benzylideneaniline **2j**, 4-methoxybenzaldehyde, *p*-tolualdehyde, and 4-nitrobenzaldehyde were purchased from Alfa Aesar (Ward Hill, MA). T3P in 2-methyltetrahydrofuran (50 weight%) was obtained from Euticals, Inc. TLC plates (silica gel GF, 250 micron, 10 x 20 cm, cat. No. 21521) were purchased from Analtech (Newark, DE) and were visualized under short wave UV, and then with I_2 and then by spraying with ceric ammonium nitrate/sulfuric acid and heating. Infrared spectra were run on a Perkin-Elmer Spectrum One using a diamond-ATR attachment for the direct powder analysis (Villanova University). Spectra were recorded at a resolution 4 cm^{-1} , 16 scans averaged. ^1H and ^{13}C NMR experiments (Penn State University Park) were carried out on a Bruker Avance-III-HD 500.20-MHz instrument using a 5 mm CPPBBO BB-1H/19F/D Z-GRD probe. Samples were dissolved in CDCl_3 and analyzed at RT. Typical conditions for ^1H acquisition were 1 sec relaxation delay, acquisition time of 2.76 sec, spectral width of 12 kHz, 16 scans. Spectra were zero-filled to 128k points, and multiplied by exponential multiplication (EM with LB = 0.3 Hz) prior to FT. For ^{13}C experiments a 2 sec relaxation delay was employed, with acquisition time of 0.9088 sec, spectral width of 36 kHz, and 128 scans. Spectra were zero-filled once, and multiplied by EM with LB = 2 Hz prior to FT. High resolution mass spectrometry was performed on an AB Sciex 5600 TripleTOF instrument (Penn State University Park). Ultraviolet/Visible

spectroscopy was performed on a Thermo Electron Corp. Genesys 10 UV (Penn State Schuylkill). Melting points were performed on an Arthur H. Thomas Co. Thomas Hoover Capillary Melting Point Apparatus (Penn State Schuylkill).

General Procedure for Preparation of Imines 2a-i, k-n. A 100-mL round bottom flask with a stir bar was charged with a substituted benzaldehyde (0.05 mol), aniline (4.56 mL, 4.66 g, 0.05 mol) and toluene (12.5 mL) and stirred. A Dean-Stark apparatus was attached and the trap was filled with toluene. The solution was heated and distilled into the trap until water was no longer being produced, generally 30 minutes or less. After cooling, the toluene was removed under vacuum. The product was recrystallized from an appropriate solvent or used crude if liquid. Recrystallization solvents, yields, and melting points (where appropriate) are reported below.

***N*-[*(2-Nitrophenyl)methylidene*]aniline (2a).** Recrystallized from EtOH to yield yellow powder (9.43 g, 83%). mp: 62-67 °C (lit. 63-64 °C⁴⁰).

***N*-[*(4-Nitrophenyl)methylidene*]aniline (2b).** Recrystallized from EtOAc/hexanes to give bright yellow crystals (8.13 g, 73%). mp: 91-93 °C (lit. 92-93 °C⁴¹).

***N*-[*(3-Nitrophenyl)methylidene*]aniline (2c).** Run on 0.034 mol scale. Recrystallized from EtOAc/hexanes to give light yellow crystals (5.48 g, 72%). mp: 64-65 °C (lit. 68-69 °C⁴²).

***N*-[*(4-(Trifluoromethyl)phenyl)methylidene*]aniline (2d).** Recrystallized from toluene to produce white crystals (4.80 g, 35%). mp: 75-76 °C (lit. 78 °C⁴³).

***N*-[*(3-(Trifluoromethyl)phenyl)methylidene*]aniline (2e).** Yellow liquid (lit. mp 47-47.5 °C⁴⁴). This crude material was used for cyclization.

***N*-[*(4-Bromophenyl)methylidene*]aniline (2f).** Recrystallized from toluene to yield white crystals (4.94 g, 38%). mp: 72-73 °C (lit. 72.5-73 °C⁴⁵).

***N*-[*(3-Bromophenyl)methylidene*]aniline (2g).** Recrystallized from cold 2-propanol to give an olive green solid, which remained solid at 6 °C but was liquid at room temperature (8.57 g, 66%). (Reported as oil.⁴⁶)

***N*-[*(4-Fluorophenyl)methylidene*]aniline (2h).** Recrystallized from hexanes to give white crystals (6.72 g, 67%). mp: 43-45 °C (lit. 44 °C⁴⁷).

***N*-[*(3-Fluorophenyl)methylidene*]aniline (2i).** Recrystallized from EtOH to produce white crystals (3.99 g, 40%). mp: 33-34 °C (lit. 33-34 °C⁴⁸).

***N*-[*(4-Methylphenyl)methylidene*]aniline (2k).** Recrystallized from hexanes to give pale yellow crystals (9.76 g, 67%). mp: 44-46 °C (lit. 49-51.5 °C⁴⁹).

***N*-[*(3-Methylphenyl)methylidene*]aniline (2l).** Brown liquid (reported as pale brown oil⁵⁰). This crude material was used for cyclization.

***N*-[*(4-Methoxyphenyl)methylidene*]aniline (2m).** Recrystallized from hexanes to give off-white powder (8.99 g, 85%). mp: 61-62 °C (lit. 63 °C⁵¹).

***N*-[*(3-Methoxyphenyl)methylidene*]aniline (2n).** Orange liquid (reported as oil⁵²). This crude material was used for cyclization.

General Procedure for Preparation of 2-Aryl-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-ones (1a-n). A two-necked 25-mL round bottom flask was oven-dried, cooled under N₂, and charged with a stir bar and an imine (6 mmol). Tetrahydrofuran or 2-methyltetrahydrofuran (2.3 mL) was added and the solution was stirred. Pyridine (1.95 mL, 24 mmol) and then thiosalicylic acid (0.931 g, 6 mmol) were added. Finally, 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P) in 2-methyltetrahydrofuran (50 weight percent; 7.3 mL, 12 mmol) was added. The reaction was stirred at room temperature at least overnight and followed by TLC, then poured into a separatory funnel with CH₂Cl₂ (20 mL). The mixture was washed with water (10 mL). The aqueous layer was then extracted twice with CH₂Cl₂ (10 mL each). The organic solutions were combined and washed with saturated NaHCO₃ (10 mL) and then saturated aq NaCl (10 mL). The organic phase was dried over sodium sulfate and concentrated under vacuum to give a crude mixture. Further purification was carried out as indicated below for each compound.

2-(2-Nitrophenyl)-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1a).¹⁹ Melting point and *R_f* previously reported.¹⁹ ¹H NMR (CDCl₃): δ (ppm): 8.25 (1H, d, ³*J* 7.3 Hz, Ar connected to C5), 8.10 (1H, d, ³*J*_{HH} 8.5 Hz), 7.63 (2H, m), 7.52 (1H, t, ³*J*_{HH} 7.3 Hz), 7.47-7.41 (3H, m), 7.36-7.32 (3H, m), 7.29 (1H, t, ³*J*_{HH} 7.3 Hz), 7.11 (1H, d, ³*J*_{HH} 8.5 Hz), 7.01 (1H, s, C2). ¹³C NMR (CDCl₃): δ (ppm): 164.3 (C=O), 146.4, 142.5, 137.5, 135.4, 133.1, 132.9, 132.8, 131.6, 130.6, 130.4, 129.5, 129.4, 128.5, 128.1, 127.8, 127.7, 126.7, 126.6, 125.8, 61.0 (C2). HRMS (*m/z*): [M+H]⁺ of 363.0794 is consistent with calculated [M+H]⁺ of 363.0798. IR (neat, cm⁻¹): 1658 (s, C=O), 1526 (s, N-O). UV/Vis (CH₃CN): λ_{max}: 275 nm (shoulder at approx. 326 nm).

2-(4-Nitrophenyl)-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1b).¹⁹ Melting point and *R_f* previously reported.¹⁹ Updated procedure: after chromatography on 30 g silica gel with mixtures of EtOAc and hexanes, recrystallization from EtOH gave off-white crystals 0.67 g (30%). ¹H NMR (CDCl₃): δ (ppm): 8.23 (1H, dd, ³*J*_{HH} 7.9, ⁴*J*_{HH} 1.3 Hz, Ar connected to C5), 8.14 (2H, d, ³*J*_{HH} 8.8 Hz), 7.63 (2H, d, ³*J*_{HH} 8.8 Hz), 7.42 (2H, m), 7.38 (1H, td, ³*J*_{HH} 7.6, ⁴*J*_{HH} 1.7 Hz), 7.33 (3H, d, ³*J*_{HH} 7.7 Hz), 7.31 (1H, m), 7.19 (1H, dd, ³*J*_{HH} 7.7, ⁴*J*_{HH} 0.7 Hz), 6.12 (1H, s, C2). ¹³C NMR (CDCl₃): δ (ppm): 163.4 (C=O), 147.7, 146.8, 142.2, 137.5, 132.9, 132.2, 131.6, 130.6, 129.5, 129.3, 127.8, 127.6, 127.5, 127.0, 125.6, 123.8, 64.6 (C2). HRMS (*m/z*): [M+H]⁺ of 363.0795 is consistent with calculated [M+H]⁺ of 363.0798. IR (neat, cm⁻¹): 1652 (s, C=O), 1515 (s, N-O). UV/Vis (CH₃CN): λ_{max}: 287 nm (shoulder at approx. 326 nm).

2-(3-Nitrophenyl)-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1c).¹⁷ Melting point and *R_f* previously reported.¹⁷ ¹H NMR (CDCl₃): δ (ppm): 8.36 (1H, s), 8.24 (1H, d, ³*J*_{HH} 9.8 Hz, Ar connected to C5), 8.12 (1H, d, ³*J*_{HH} 6.1 Hz), 7.79 (1H, d, ³*J*_{HH} 7.3 Hz), 7.49-7.29 (8H, m), 7.20 (1H, d, ³*J*_{HH} 7.3 Hz), 6.14 (1H, s, C2). ¹³C NMR (CDCl₃): δ (ppm): 163.4 (C=O), 148.4, 142.2, 142.0, 132.8, 132.3, 132.1, 130.7, 129.52, 129.48, 129.4, 127.8, 127.6, 127.0, 125.8, 123.3, 121.7, 64.6 (C2). HRMS (*m/z*): [M+H]⁺ of 363.0796 is consistent with calculated [M+H]⁺ of 363.0798. IR (neat, cm⁻¹): 1654 (s, C=O), 1520 (s, N-O). UV/Vis (CH₃CN): 281 nm (shoulder at approx. 317 nm).

3-Phenyl-2-[4-(trifluoromethyl)phenyl]-2,3-dihydro-4H-1,3-benzothiazin-4-one (1d). After chromatography on 30 g silica gel with mixtures of EtOAc and hexanes, recrystallization from isopropanol/water gave fine white crystals, 0.87 g (38%), mp: 137-139 °C. R_f (20% EtOAc/hexanes): 0.50. ^1H NMR (CDCl_3): δ (ppm): 8.24 (1H, d, $^3J_{\text{HH}}$ 7.3 Hz, Ar connected to C5), 7.57 (4H, t, $^3J_{\text{HH}}$ 8.5 Hz), 7.43-7.29 (7H, m, 7.19 (1H, d, $^3J_{\text{HH}}$ 8.5 Hz), 6.08 (1H, s, C2). ^{13}C NMR (CDCl_3): δ (ppm): 163.6 (C=O), 143.7, 142.3, 132.7, 132.6, 130.5, 130.4 (q, $^2J_{\text{CF}}$ 32.6 Hz, Ar C connected to CF_3), 129.4, 127.8, 127.4, 126.9, 126.8, 125.7, 125.5 (q, $^3J_{\text{CF}}$ 3.7 Hz, Ar *ortho* to CF_3), 1243.8 (q, $^1J_{\text{CF}}$ 271.7 Hz, CF_3), 64.8 (C2). HRMS (m/z): $[\text{M}+\text{H}]^+$ of 386.0814 is consistent with calculated $[\text{M}+\text{H}]^+$ of 386.0821. IR (neat, cm^{-1}): 1651 (s, C=O). UV/Vis (CH_3CN): λ_{max} : 278 nm (shoulder at approx. 314 nm).

3-Phenyl-2-[3-(trifluoromethyl)phenyl]-2,3-dihydro-4H-1,3-benzothiazin-4-one (1e). The imine was used as a crude liquid. After chromatography on 30 g silica gel with mixtures of EtOAc and hexanes, the material was triturated with hexanes to give a pale yellow solid, 0.4959 g. Recrystallization from cyclohexane gave white flakes, 0.28 g (12%), mp: 114-115 °C. R_f (25% EtOAc/hexanes): 0.50. ^1H NMR (CDCl_3): δ (ppm): 8.23 (1H, d, $^3J_{\text{HH}}$ 7.6 Hz, Ar connected to C5), 7.71 (1H, s), 7.63 (1H, d, $^3J_{\text{HH}}$ 7.3 Hz), 7.51 (1H, d, $^3J_{\text{HH}}$ 7.3 Hz), 7.41-7.29 (8H, m), 7.20 (1H, d, $^3J_{\text{HH}}$ 7.6 Hz), 6.10 (1H, s, C2). ^{13}C NMR (CDCl_3): δ (ppm): 163.6, 142.3, 140.7, 132.7, 131.42-130.64 (q, $^2J_{\text{CF}}$ 32.7 Hz, Ar C connected to CF_3), 130.5, 129.7; 129.43, 129.41, 129.0, 127.8, 127.5, 126.8, 125.8, 125.24-125.15 (q, $^3J_{\text{CF}}$ 3.5 Hz), 123.55-123.46 (q, $^3J_{\text{CF}}$ 4.0 Hz, Ar *ortho* to CF_3); 127.0, 124.8, 122.6, and 120.5 (q, $^1J_{\text{CF}}$ 272.7 Hz, CF_3 , Ar *ortho* to CF_3); 64.9 (C2), 26.9. HRMS (m/z): $[\text{M}+\text{H}]^+$ of 386.0817 is consistent with calculated $[\text{M}+\text{H}]^+$ of 386.0821. IR (neat, cm^{-1}): 1649 (s, C=O). UV/Vis (CH_3CN): λ_{max} : 275 nm (shoulder at approx. 314 nm).

2-(4-Bromophenyl)-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1f). After chromatography on 30 g silica gel with mixtures of EtOAc and hexanes, recrystallization from isopropanol gave fine off-white crystals, 0.83 g (35%), mp: 148-151 °C. R_f (30% EtOAc/hexanes): 0.50. ^1H NMR (CDCl_3): δ (ppm): 8.22 (1H, d, $^3J_{\text{HH}}$ 7.3 Hz, Ar connected to C5), 7.40 (4H, t, $^3J_{\text{HH}}$ 7.9 Hz), 7.37-7.27 (7H, m), 7.19 (1H, d, $^3J_{\text{HH}}$ 8.5 Hz), 6.01 (1H, s, C2). ^{13}C NMR (CDCl_3): δ (ppm): 163.6 (C=O), 142.3, 138.7, 132.9, 132.6, 131.6, 130.5, 129.4, 129.3, 128.3, 127.8, 127.3, 126.6, 125.7, 122.4, 64.8 (C2). HRMS (m/z): $[\text{M}+\text{H}]^+$ of 396.0049 for ^{79}Br is consistent with calculated $[\text{M}+\text{H}]^+$ of 396.0052 and $[\text{M}+\text{H}]^+$ of 398.0032 for ^{81}Br is consistent with calculated $[\text{M}+\text{H}]^+$ of 398.0032. IR (neat, cm^{-1}): 1646 (s, C=O). UV/Vis (CH_3CN): λ_{max} : 275 nm (shoulder at approx. 314 nm).

2-(3-Bromophenyl)-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1g). After chromatography on 30 g silica gel with mixtures of EtOAc and hexanes, recrystallization from MeOH gave tan crystals, 0.54 g (23%), mp: 118-120 °C. R_f (30% EtOAc/hexanes): 0.49. ^1H NMR (CDCl_3): δ (ppm): 8.23 (1H, d, $^3J_{\text{HH}}$ 9.8 Hz, Ar connected to C5), 7.60 (1H, s), 7.42-7.28 (9H, m), 7.20 (1H, d, $^3J_{\text{HH}}$ 7.3 Hz), 7.15 (1H, m), 6.01 (1H, s, C2). ^{13}C NMR (CDCl_3): δ (ppm): 163.6 (C=O), 142.3, 141.9, 132.8, 132.6, 131.5, 130.5, 129.9, 129.7, 129.40, 129.36, 127.8, 127.4, 126.7, 125.8, 125.2, 122.7, 64.6 (C2). HRMS (m/z): $[\text{M}+\text{H}]^+$ of 396.0051 for ^{79}Br is consistent with calculated $[\text{M}+\text{H}]^+$ of 396.0052 and $[\text{M}+\text{H}]^+$ of 398.0031 for ^{81}Br is consistent with calculated

[M+H]⁺ of 398.0032. IR (neat, cm⁻¹): 1652 (s, C=O). UV/Vis (CH₃CN): 278 nm (shoulder at approx. 317 nm).

2-(4-Fluorophenyl)-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1h). After chromatography on 30 g silica gel with mixtures of EtOAc and hexanes, recrystallization from EtOH/water gave white crystals, 0.30 g (15%), mp: 100-105 °C. *R_f* (30% EtOAc/hexanes): 0.54. ¹H NMR (CDCl₃): δ (ppm): 8.23 (1H, d, ³*J*_{HH} 8.1 Hz, Ar connected to C5), 7.43-7.27 (9H, m), 7.20 (1H, d, ³*J*_{HH} 7.7 Hz), 6.96 (2H, triplet, ³*J*_{HH}, ³*J*_{HF} 8.3 Hz), 6.06 (1H, s, C2). ¹³C NMR (CDCl₃): δ (ppm): 163.7 (C=O); 163.26 and 161.62 (d, ¹*J*_{CF} 248.5 Hz, C-F); 142.3, 135.23 and 135.21 (d, ⁴*J*_{CF} 3.3 Hz Ar *para* to CF); 133.1, 132.5, 130.5, 129.4, 129.3; 128.44 and 128.38 (d, ³*J*_{CF} 8.8 Hz Ar *meta* to CF); 127.7, 127.3, 126.5, 125.8; 115.54 and 115.39 (d, ²*J*_{CF} 22.0 Hz, Ar *ortho* to CF); 64.8 (C2). HRMS (*m/z*): [M+H]⁺ of 336.0846 is consistent with calculated [M+H]⁺ of 336.0853. IR (neat, cm⁻¹): 1648 (s, C=O). UV/Vis (CH₃CN): 272 nm (shoulder at approx. 314 nm).

2-(3-Fluorophenyl)-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1i). After chromatography on 30 g silica gel with mixtures of EtOAc and hexanes, recrystallization from dichloromethane/hexanes gave off-white powder, 0.86 g (43%), mp: 102-103 °C. *R_f* (20% EtOAc/hexane): 0.33. ¹H NMR (CDCl₃): δ (ppm): 8.23 (1H, dd, ³*J*_{HH} 7.8, ⁴*J*_{HH} 1.1 Hz, Ar connected to C5), 7.42-7.16 (11H, m), 6.95 (1H, apparent t with fine splitting), 6.04 (1H, s, C2). ¹³C NMR (CDCl₃): δ (ppm): 163.7 and 161.7 (d, ¹*J*_{CF} 248 Hz, C-F); 163.6 (C=O); 142.4; 142.29 and 142.24 (d, ³*J*_{CF} 7.3 Hz, Ar *meta* to CF); 135.7, 130.5; 130.03 and 129.97 (d, ³*J*_{CF} 8.2 Hz Ar *meta* to CF); 129.4, 129.3, 127.7, 127.3, 126.6, 125.8; 125.35 and 122.33 (d, ⁴*J*_{CF} 2.8 Hz, Ar *para* to CF); 115.48 and 115.32 (d, ²*J*_{CF} 20.9 Hz Ar *ortho* to CF); 114.00 and 113.81 (d, ²*J*_{CF} 23.6 Hz, Ar *ortho* to CF); 64.8 (d, ⁴*J*_{CF} 2 Hz, C2). HRMS (*m/z*): [M+H]⁺ of 336.0856 is consistent with calculated [M+H]⁺ of 336.0853. IR (neat, cm⁻¹): 1647 (s, C=O). UV/Vis (CH₃CN): λ_{max}: 275 nm (shoulder at approx. 314 nm).

2,3-Diphenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1j).^{13,18} All data previously reported.¹³ New measurements of UV-Visible spectrum: λ_{max} (CH₃CN): 272 (shoulder at approx. 308) nm. λ_{max} (cyclohexane): 275 nm (shoulder at approx. 314 nm)

2-(4-Methylphenyl)-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1k). Hot filtration in EtOH followed by recrystallization from toluene/hexanes gave yellowish crystals, 0.57 g (30%), mp: 108-111 °C. *R_f* (20% EtOAc/hexanes): 0.34. ¹H NMR (CDCl₃): δ (ppm): 8.24 (1H, d, ³*J*_{HH} 8.1 Hz, Ar connected to C5), 7.39-7.25 (10H, m), 7.18 (1H, d, ³*J*_{HH} 7.7 Hz), 7.08 (1H, d, ³*J*_{HH} 7.7 Hz), 6.03 (1H, s, C2), 2.30 (3H, s, CH₃). ¹³C NMR (CDCl₃): δ (ppm): 163.8 (C=O), 142.6, 138.1, 136.5, 133.4, 132.4, 130.4, 129.5, 129.19, 129.17, 127.7, 127.1, 126.5, 126.3, 125.9, 65.1 (C2), 21.0 (CH₃). HRMS (*m/z*): [M+H]⁺ of 332.1104 is consistent with calculated [M+H]⁺ of 332.1104. IR (neat, cm⁻¹): 1646 (s, C=O). UV/Vis (CH₃CN): λ_{max}: 278 nm (shoulder at approx. 314 nm).

2-(3-Methylphenyl)-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1l). The imine was used as a crude liquid. After chromatography on 30 g silica gel with mixtures of EtOAc and hexanes, recrystallization from acetonitrile/water gave colorless crystals (0.31 g, 16% from crude imine), mp: 91-95 °C. *R_f* (15% EtOAc/hexanes): 0.25. ¹H NMR (CDCl₃): δ (ppm): 8.24 (1H, d, ³*J*_{HH} 8.5 Hz, Ar connected to C5), 7.40-7.34 (5H, m), 7.30-7.26 (2H, m), 7.23 (2H, s), 7.18 (2H,

m), 7.06 (1H, d, $^3J_{\text{HH}}$ 7.3 Hz), 6.02 (1H, s, C2), 2.30 (3H, s, CH₃). ^{13}C NMR (CDCl₃): δ (ppm): 163.8 (C=O), 142.6, 139.4, 138.3, 133.3, 132.4, 130.4, 129.5, 129.2, 129.1, 128.3, 127.7, 127.3, 127.1, 126.3, 125.9, 123.7, 65.2 (C2), 21.5 (CH₃). HRMS (m/z): $[\text{M}+\text{H}]^+$ of 332.1098 is consistent with calculated $[\text{M}+\text{H}]^+$ of 332.1104. IR (neat, cm⁻¹): 1648 (s, C=O). UV/Vis (CH₃CN): λ_{max} : 278 nm (shoulder at approx. 314 nm).

2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1m). After chromatography on 30 g silica gel with mixtures of EtOAc and hexanes, recrystallization from EtOH gave fine white solid, 0.70 g. Recrystallization of the solid from dichloromethane/hexanes produced shiny white crystals, 0.67 g (32%). mp: 136.5-139.5 °C R_f (40% EtOAc/hexanes): 0.48. ^1H NMR (CDCl₃): δ (ppm): 8.23 (1H, dd, $^3J_{\text{HH}}$ 8.1, $^4J_{\text{HH}}$ 1.1 Hz, Ar connected to C5), 7.39-7.34 (7H, m), 7.29-7.26 (2H, m), 7.19 (1H, m), 6.80 (2H, m), 6.04 (1H, s, C2), 3.76 (3H, s, OCH₃). ^{13}C NMR (CDCl₃): δ (ppm): 163.8 (C=O), 159.4, 142.5, 133.5, 132.4, 131.6, 131.3, 130.4, 129.5, 129.2, 127.9, 127.7, 127.1, 126.3, 125.9, 113.8, 65.0 (C2), 55.3 (OCH₃). HRMS (m/z): $[\text{M}+\text{H}]^+$ of 348.1046 is consistent with calculated $[\text{M}+\text{H}]^+$ of 348.1053. IR (neat, cm⁻¹): 1645 (s, C=O). UV/Vis (CH₃CN): λ_{max} : 284 nm (shoulder at approx. 314 nm).

2-(3-Methoxyphenyl)-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1n). The imine was used as a crude liquid. After chromatography on 30 g silica gel with mixtures of EtOAc and hexanes, recrystallization from EtOH gave fine white crystals, 0.84 g (40% from crude imine), mp: 125-127 °C. R_f (30% EtOAc/hexanes): 0.44. ^1H NMR (CDCl₃): δ (ppm): 8.23 (1H dd, $^3J_{\text{HH}}$ 7.9, $^4J_{\text{HH}}$ 1.3 Hz, Ar connected to C5), 7.40-7.34 (5H, m), 7.30-7.26 (2H, m), 7.19 (2H, m), 7.01 (1H, m), 6.97 (1H, m), 6.79 (1H, dd, $^3J_{\text{HH}}$ 8.3 Hz, $^4J_{\text{HH}}$ 2.4 Hz), 6.02 (1H, s, C2), 3.74 (3H, s, OCH₃). ^{13}C NMR (CDCl₃): δ (ppm): 163.8 (C=O), 159.6, 142.5, 141.1, 133.3, 132.4, 130.4, 129.6, 129.5, 129.2, 127.7, 127.2, 126.4, 125.9, 119.1, 113.8, 112.4, 65.2 (C2), 55.2 (OCH₃). HRMS (m/z): $[\text{M}+\text{H}]^+$ of 348.1045 is consistent with calculated $[\text{M}+\text{H}]^+$ of 348.1053. IR (neat, cm⁻¹): 1653 (s, C=O). UV/Vis (CH₃CN): λ_{max} : 278 nm (shoulder at approx. 314 nm).

Acknowledgements

The authors thank SP Controls, Inc. for summer support of RVB and ASC; Euticals, Inc. for the gift of T3P in 2-methyltetrahydrofuran; Dr. Phillip Smith (Penn State University Park Metabolomics Core Facility, grant NSF MRI 1126373) for HRMS analyses; and Penn State Schuylkill for financial support.

Supplementary Material

^1H NMR, ^{13}C NMR, and FTIR spectra.

References

1. Jeng, F.; Li, X.; Shao, J.; Zhu, M.; Li, Y.; Hua, C.; Xiaoliu, L. *Chin. J. Org. Chem.* **2015**, *35*, 1370-1374.
<http://dx.doi.org/10.6023/cjoc201412053>
2. Hou, Y.; Xing, S.; Shao, J.; Yin, Z.; Hao, L.; Yang, T.; Zhang, H.; Zhu, M.; Chen, H.; Li, X. *Carbohydr. Res.* **2016**, *429*, 105-112, and references cited therein.
<http://dx.doi.org/10.1016/j.carres.2016.02.011>
3. Li, Q.; Li, C.; Lu, X.; Zhang, H.; Zhu, H. *Eur. J. Med. Chem.* **2012**, *50*, 288-295.
<http://dx.doi.org/10.1016/j.ejmech.2012.02.007>
4. Wang, S.; Fang, K.; Dong, G.; Chen, S.; Liu, N.; Miao, Z.; Yao, J.; Li, J.; Zhang, W.; Sheng, C. *J. Med. Chem.* **2015**, *58*, 6678-6696.
<http://dx.doi.org/10.1021/acs.jmedchem.5b00910>
5. Kamel, M. M.; Ali, H. I.; Anwar, M. M.; Mohamed, N. A.; Soliman, A. M. M. *Eur. J. Med. Chem.* **2010**, *45*, 572.
<http://dx.doi.org/10.1016/j.ejmech.2009.10.044>
6. Popiolek, L.; Biernasiuk, A.; Malm, A. *J. Heterocycl. Chem.* **2016**, *53*, 479-486, and references cited therein.
<http://dx.doi.org/10.1002/jhet.2429>
7. Mei, Z.; Wang, L.; Lu, W.; Pang, C.; Maeda, T.; Peng, W.; Kaiser, M.; El Sayed, I.; Inokuchi, T. *J. Med. Chem.* **2013**, *56*, 1431-1442.
<http://dx.doi.org/10.1021/jm300887b>
8. Nofal, Z. M.; Soliman, E. A.; El-Karim, A.; El-Zahar, M. I.; Srouf, A. M.; Sethumadhavan, S.; Maher, T. J. *J. Heterocycl. Chem.* **2014**, *51*, 1797-1806.
<http://dx.doi.org/10.1002/jhet.1886>
9. Zarghi, A.; Zebardast, T.; Daraie, B.; Hedayati, M. *Bioorg. Med. Chem.* **2009**, *17*, 5369-5373.
<http://dx.doi.org/10.1016/j.bmc.2009.06.056>
10. Mandour, A. H.; El-Sawy, E. R.; Ebid, M. S.; El-Sayed, Z. G. *Egypt. J. Chem.* **2007**, *50*, 555-568.
11. Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347-361.
<http://dx.doi.org/10.1016/j.cbpa.2010.02.018>
12. Li, S.; Hong, H.; Zhu, N.; Han, L.; Lü, J. *Chin. J. Org. Chem.* **2016**, *36*, 2024-2038.
<http://dx.doi.org/10.6023/cjoc201603034>
13. Silverberg, L. J.; Pacheco, C. N.; Lagalante, A.; Cannon, K. C.; Bachert, J. T.; Xie, Y.; Baker, L.; Bayliff, J. A. *Intl. J. Chem. (Toronto, ON, Can.)* **2015**, *7* (2), 150-162, and references cited therein.
<http://dx.doi.org/10.5539/ijc.v7n2p150>
14. Dandia, A.; Saha, M.; Taneja, H. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, *139*, 77-85.
<http://dx.doi.org/10.1080/10426509808035677>

15. Bajpai, S. N.; Joshi, K. C.; Jain, R. *Heterocycl. Commun.* **1997**, *3*, 41-46.
<http://dx.doi.org/10.1515/HC.1997.3.1.41>
16. Kitsiou, C.; Unsworth, W. P.; Coulthard, G.; Taylor, R. J. K. *Tetrahedron* **2014**, *70*, 7172.
<http://dx.doi.org/10.1016/j.tet.2014.04.066>
17. Yennawar, H. P.; Silverberg, L. J.; Minehan, M. J.; Tierney, J. *Acta Cryst.* **2013**, *E69*, o1679.
<http://dx.doi.org/10.1107/S1600536813028389>
18. Yennawar, H. P.; Bendinsky, R. V.; Coyle, D. J.; Cali, A. S.; Silverberg, L. J. *Acta Cryst.* **2014**, *E70*, o465 and references cited therein.
<http://dx.doi.org/10.1107/S1600536814005881>
19. Yennawar, H. P.; Cali, A. S.; Xie, Y. Silverberg, L. J. *Acta Cryst.* **2015**, *E71*, 414-417.
<http://dx.doi.org/10.1107/S2056989015004545>
20. Dandia, A.; Saha, M.; Shivpuri, A. *Ind. J. Chem. Tech.* **1997**, *4*, 201-205.
21. Jain, R.; Vajpei, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **1992**, *70*, 63-66.
<http://dx.doi.org/10.1080/10426509208049152>
22. Abdel-Rahman, R. M.; Fawzy, M. M. *Asian J. Chem.* **1992**, *4*, 621-628.
23. Joshi, K. C.; Jain, R.; Nishith, S. *J. Ind. Chem. Soc.* **1991**, *68*, 625-627.
24. Heindel, N. D.; Fish, V. B.; Ryan, M. F.; Lepley, A. R. *J. Org. Chem.* **1967**, *32*, 2678-2681.
<http://dx.doi.org/10.1021/jo01284a006>
25. Silverberg, L. J.; Yennawar, H. P.; Coyle, D. J.; Noble, D. J.; Yang, Z. *Acta Cryst.* **2016**, *E72*, 1108-1112.
<http://dx.doi.org/10.1107/S2056989016011002>
26. Tierney, J.; Houghton, G.; Sanford, K.; Mascavage, L.; McCoy, M.; Findeisen, A.; Kilburn. *J. Magn. Reson. Chem.* **1996**, *34*, 573-576.
[http://dx.doi.org/10.1002/\(SICI\)1097-458X\(199608\)34:8<573::AID-OMR928>3.0.CO;2-D](http://dx.doi.org/10.1002/(SICI)1097-458X(199608)34:8<573::AID-OMR928>3.0.CO;2-D)
27. Woolston, C. R. J.; Lee, J. B.; Swinbourne, F. J.; Thomas, W. A. *Magn. Reson. Chem.* **1992**, *30*, 1075-1078.
<http://dx.doi.org/10.1002/mrc.1260301109>
28. Marques, M. P.; Amorim da Costa, A. M.; Ribeiro-Claro, P. J. A. *J. Phys. Chem. A* **2001**, *105*, 5292-5297.
<http://dx.doi.org/10.1021/jp0046041>
29. Müller, K.; Faeh, C.; Diederich, F. *Science*, **2007**, *317* (5486), 1881-1886.
<http://dx.doi.org/10.1126/science.1131943>
30. Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonek, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422-518.
<http://dx.doi.org/10.1021/acs.chemrev.5b00392>
31. Facey, G. <http://u-of-o-nmr-facility.blogspot.com/2007/10/13c-nmr-of-fluorinated-organics.html> accessed August 20, 2016.
32. Hoffman, R. <http://chem.ch.huji.ac.il/nmr/whatisnmr/hetcoup.htm> accessed August 20, 2016.

33. Glaser, R. E. http://faculty.missouri.edu/~glaserr/8160f09/fluoroacetone_NMR.pdf accessed August 20, 2016.
34. Foris, A. *Magn. Reson. Chem.* **2004**, 42, 534-555.
<http://dx.doi.org/10.1002/mrc.1368>
35. Newmark, R. A.; Hill, J. R. *Org. Magn. Resonance* **1977**, 9, 589.
36. Aguilar, J. A.; Morrisb, G. A.; Kenwright, A. M. *RSC Adv.* **2014**, 4, 8278-8282.
<http://dx.doi.org/10.1039/c3ra46745g>
37. Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, 93, 2361-2369.
<http://dx.doi.org/10.1021/ja00739a001>
38. Woolston, C. R. J.; Lee, J. B.; Swinbourne, F. J. *Magn. Reson. Chem.* **1993**, 31, 348-351.
<http://dx.doi.org/10.1002/mrc.1260310407>
39. Alvarez, S. *Dalton Trans.* **2013**, 42, 8617-8636.
<http://dx.doi.org/10.1039/C3DT50599E>
40. Creencia, E. C.; Kosaka, M.; Muramatsu, M.; Kobayashi, M.; Iizuki, T.; Haraguchi, T. *J. Heterocycl. Chem.* **2009**, 46, 1309-1317.
<http://dx.doi.org/10.1002/jhet.267>
41. Forlani, L.; Sintoni, M.; Todesco, P. E. *Gazz. Chim. Ital.* **1986**, 116, 229-232.
42. Steevens, J. B.; Pandit, U. K. *Tetrahedron* **1983**, 39, 1395-4000.
[http://dx.doi.org/10.1016/S0040-4020\(01\)91910-6](http://dx.doi.org/10.1016/S0040-4020(01)91910-6)
43. Titov, V. E.; Bondarenko, V. N.; Koshechko, V. G.; Pokhodenko, V. D. *Theor. Exp. Chem.* **2008**, 44, 271-277.
<http://dx.doi.org/10.1007/s11237-008-9038-5>
44. Maginnity, P. M.; Eisenmann, J. L. *J. Am. Chem. Soc.* **1952**, 74, 6119-6121.
<http://dx.doi.org/10.1021/ja01143a518>
45. Weinstein, J.; McIninch, E. *J. Am. Chem. Soc.* **1960**, 82, 6064-6067.
<http://dx.doi.org/10.1021/ja01508a023>
46. Azizi, N.; Edrisi, M. *Monatsh. Chem.* **2015**, 146, 1695-1698.
<http://dx.doi.org/10.1007/s00706-015-1447-2>
47. Sobhanov, A. A.; Zolotukhin, A. V.; Galkino, I. V.; Galkin, V. I.; Cherkasov, R. A. *Russ. J. Gen. Chem.* **2006**, 76, 421-429.
<http://dx.doi.org/10.1134/S1070363206030121>
48. Koshechko, V. G.; Titov, V. E.; Bondarenko, V. N.; Pokhodenko, V. D. *J. Fluorine Chem.* **2008**, 129, 701-706.
<http://dx.doi.org/10.1016/j.jfluchem.2008.06.010>
49. Anders, E. J.; Tropsch, J. G.; Katritzky, A. R.; Rasala, D.; Vanden Eynde, J. J. *J. Org. Chem.* **1989**, 54, 4808-4812.
<http://dx.doi.org/10.1021/jo00281a021>
50. Law, H. D. *J. Chem. Soc. Trans.* **1912**, 101, 154-66.
<http://dx.doi.org/10.1039/CT9120100154>

51. O'Boyle, N.; Carr, M.; Greene, L. M.; Bergin, O.; Nathwani, S. M.; McCabe, T.; Lloyd, D. G.; Zisterer, D. M.; Meegan, M. J. *J. Med. Chem.* **2010**, 53, 8569-8584.
<http://dx.doi.org/10.1021/jm101115u>
52. Shetty, B. V.; McFadden, A.; Hofer, P. U.S. Patent 4 476 311, 1984.