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

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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.\(^1\)

\[
\begin{align*}
\text{Figure 1.} & \quad \text{2,3-Dihydro-}4H-1,3\text{-benzothiazin-4-one skeleton (}R^1 = H, \text{ alkyl, aryl, heteroaryl, } R^2 = \text{ alkyl, aryl, heteroaryl).}
\end{align*}
\]

A variety of methods have been reported for the synthesis of 2,3-dihydro-4\(H\)-1,3-benzothiazin-4-ones.\(^1\) 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 \(\text{Na}_2\text{SO}_4/1,4\)-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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.

\textbf{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 Tierney\textsuperscript{26} and Woolston\textsuperscript{27} for meta- and para-substituted 2-aryl-3-phenyl-1,3-thiazolidin-4-ones (five-membered heterocycles).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{1H_NMR_Chemical_Shifts_at_C2.png}
\caption{\textsuperscript{1}H chemical shifts at C2 (ppm, CDCl\textsubscript{3}) (2-aryl moiety substitution: orange = unsubstituted, red = para-substituted, blue = meta-substituted, green = ortho-substituted).}
\end{figure}
Scheme 1. Preparation of 2-aryl-3-phenyl-2,3-dihydro-4H-1,3-benzothiazin-4-ones.

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield of 1 from 2 (%)</th>
<th>(^{1})H NMR Chemical Shifts at C2 (ppm, CDCl(_3))</th>
<th>(^{13})C NMR Chemical Shifts at C2 (ppm, CDCl(_3))</th>
<th>(^{13})C NMR Chemical Shifts at C4 (ppm, CDCl(_3))</th>
<th>IR Absorbance of Carbonyl (C4) (cm(^{-1}))</th>
<th>UV/Vis (\lambda_{\text{max}}) and approx. (\lambda_{\text{max}}) or shoulder peak (CH(_3)CN) (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a(^{19})</td>
<td>(o)-NO(_2)</td>
<td>14(^{a})</td>
<td>7.01</td>
<td>61.0</td>
<td>164.3</td>
<td>1658</td>
<td>275, 326</td>
</tr>
<tr>
<td>1b(^{19})</td>
<td>(p)-NO(_2)</td>
<td>30(^{b})</td>
<td>6.12</td>
<td>64.6</td>
<td>163.4</td>
<td>1652</td>
<td>287, 326</td>
</tr>
<tr>
<td>1c(^{17})</td>
<td>(m)-NO(_2)</td>
<td>40(^{b})</td>
<td>6.14</td>
<td>64.6</td>
<td>163.4</td>
<td>1654</td>
<td>281, 317</td>
</tr>
<tr>
<td>1d</td>
<td>(p)-CF(_3)</td>
<td>38(^{b})</td>
<td>6.08</td>
<td>64.8</td>
<td>163.6</td>
<td>1651</td>
<td>278, 314</td>
</tr>
<tr>
<td>1e</td>
<td>(m)-CF(_3)</td>
<td>12(^{c,e})</td>
<td>6.10</td>
<td>64.9</td>
<td>163.6</td>
<td>1649</td>
<td>275, 314</td>
</tr>
<tr>
<td>1f</td>
<td>(p)-Br</td>
<td>35(^{b})</td>
<td>6.01</td>
<td>64.8</td>
<td>163.6</td>
<td>1646</td>
<td>275, 314</td>
</tr>
<tr>
<td>1g</td>
<td>(m)-Br</td>
<td>23(^{b})</td>
<td>6.01</td>
<td>64.6</td>
<td>163.6</td>
<td>1652</td>
<td>278, 317</td>
</tr>
<tr>
<td>1h</td>
<td>(p)-F</td>
<td>15(^{b})</td>
<td>6.06</td>
<td>64.8</td>
<td>163.7</td>
<td>1648</td>
<td>272, 314</td>
</tr>
<tr>
<td>1i</td>
<td>(m)-F</td>
<td>43(^{b})</td>
<td>6.04</td>
<td>64.8</td>
<td>163.6</td>
<td>1647</td>
<td>275, 314</td>
</tr>
<tr>
<td>1j(^{13,18})</td>
<td>H</td>
<td>35(^{b})</td>
<td>6.07(^{13})</td>
<td>65.3(^{13})</td>
<td>163.8(^{13})</td>
<td>1682(^{13})</td>
<td>275, 314</td>
</tr>
<tr>
<td>1k</td>
<td>(p)-Me</td>
<td>30(^{d})</td>
<td>6.03</td>
<td>65.1</td>
<td>163.8</td>
<td>1646</td>
<td>278, 314</td>
</tr>
<tr>
<td>1l</td>
<td>(m)-Me</td>
<td>16(^{a,e})</td>
<td>6.02</td>
<td>65.2</td>
<td>163.8</td>
<td>1648</td>
<td>278, 314</td>
</tr>
<tr>
<td>1m</td>
<td>(p)-OMe</td>
<td>32(^{a})</td>
<td>6.04</td>
<td>65.0</td>
<td>163.8</td>
<td>1645</td>
<td>284, 314</td>
</tr>
<tr>
<td>1n</td>
<td>(m)-OMe</td>
<td>40(^{a,e})</td>
<td>6.02</td>
<td>65.2</td>
<td>163.8</td>
<td>1653</td>
<td>278, 314</td>
</tr>
</tbody>
</table>

*a*Isolated by chromatography and then two recrystallizations. *b*Isolated by chromatography and then recrystallization. *c*Isolated by chromatography, then trituration with hexanes, and then recrystallization. *d*Isolated by hot filtration in EtOH and then recrystallization from toluene/hexanes. *e*The imine 2 was used as a crude liquid.
**Hammett correlation attempts**

Attempts were made to correlate $^1$H and $^{13}$C substituent chemical shifts with Hammett $\sigma$ 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 $\lambda_{max}$ values were plotted against Hammett $\sigma$ constants. It is believed that the more complex structure and competing electronic influences within the fused 2,3-diaryl-2,3-dihydro-4H-1,3-benzothiazin-4-ones is the reason for the absence of clear correlations as witnessed by Tierney$^{26}$ and Woolston$^{27}$ 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.$^{19}$](image-url)
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.\textsuperscript{29,30} The other is the potential to exploit \( ^1\text{H}-^{19}\text{F} \) and \( ^{13}\text{C}-^{19}\text{F} \) spin-spin coupling (\( ^nJ_{HF} \) and \( ^nJ_{CF} \)) for \( ^1\text{H} \) and \( ^{13}\text{C} \) chemical shift assignments in NMR spectroscopy.\textsuperscript{31-37}

The \( p \)-fluoro compound \( 1h \) showed a signal at 6.96 ppm for the two hydrogens \textit{ortho} to the fluorine. The signal displayed a triplet pattern with \( \sim 8.3 \) Hz separation between the peaks. This separation is believed to stem from the \( ^3J_{HH} \) and \( ^3J_{HF} \) couplings of the \textit{ortho} proton to the \textit{meta} (with respect to F) and to the fluorine itself, respectively. The \( ^3J_{HH} \) and \( ^3J_{HF} \) 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 \textit{para} to the thiazine ring and \textit{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 \( ^1\text{H}-^{19}\text{F} \) coupling.

\textbf{\( ^{13}\text{C} \) NMR Spectroscopy}

There was very little variation in the \( C_4 \) (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 \textit{meta}- and \textit{para}-substituted compounds is similar to that seen for 2-aryl-3-phenyl-1,3-thiazolidin-4-ones by Tierney\textsuperscript{26} and Woolston.\textsuperscript{38} Among the \textit{meta}- and \textit{para}-substituted compounds, the chemical shift values increased as electron withdrawing decreased and electron donation increased.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{13C_NMR_Chemical_Shifts_C4_CDCl3.png}
\caption{\textsuperscript{13}C chemical shifts at C4 (ppm, CDCl\textsubscript{3}) (2-aryl moiety substitution: orange = unsubstituted, red = \textit{para}-substituted, blue = \textit{meta}-substituted, green = \textit{ortho}-substituted).}
\end{figure}
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.

![13C NMR Chemical Shifts at C2 (ppm, CDCl3)](image)

**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
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 ($^4J_{CF} = 2$ Hz). The coupling constants for the aromatic carbons in all cases were close to the expected values of ~250 Hz for the ipso carbon ($^1J_{CF}$), ~20 Hz for the ortho carbons ($^2J_{CF}$), ~8 Hz for the meta carbons ($^3J_{CF}$) and ~3 Hz for the para-carbon ($^4J_{CF}$). \(^{37}\)
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 $^1J_{CF}$, 32.7 Hz for $^2J_{CF}$, and between 3 and 4 Hz for $^3J_{CF}$, all as expected. In the p-trifluoromethyl compound 1d three C-F couplings were observed, also from the CF$_3$ carbon ($^1J_{CF}$ = 271.7 Hz), the aromatic carbon connected to it ($^2J_{CF}$ = 32.6 Hz), and one signal for the two ortho carbons ($^3J_{CF}$ = 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$^{-1}$, 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.

![IR at C4 (cm$^{-1}$)](image)

**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 $\lambda_{\text{max}}$ 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. 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 $\lambda_{\text{max}}$ in CH$_3$CN 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-4H-1,3-thiazin-4-one, so it is apparently due to the fused benzene ring.

![Figure 10. UV Absorptions at $\lambda_{\text{max}}$ (nm) (2-aryl moiety substitution: orange = unsubstituted, red = para-substituted, blue = meta-substituted, green = ortho-substituted).](image)

**Nitro compounds**
The nitro series **1a-c** showed increasing $\lambda_{\text{max}}$ progressing from *ortho* to *meta* to *para*. 
Conclusions

A series of novel 2-aryl-3-phenyl-2,3-dihydro-4\(^{\text{H}}\)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 \(^{1}\text{H}\) and \(^{13}\text{C}\) NMR signals at C2, and the same was true of the \(^{13}\text{C}\) 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 \(^{13}\text{C}\) NMR signals for C2 and C4 generally increased. The o-nitro compound 1a displayed through-space interactions in the \(^{1}\text{H}\) and \(^{13}\text{C}\) NMR spectra, consistent with the X-ray structure. The fluorinated compounds 1f, 1g, 1d, and 1e displayed \(^{13}\text{C}\)-\(^{19}\text{F}\) couplings and 1h and 1i also showed \(^{1}\text{H}\)-\(^{19}\text{F}\) 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-ary1-2-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. \(^{1}\text{H}\) and \(^{13}\text{C}\) 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 \(^{1}\text{H}\) 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 \(^{13}\text{C}\) 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.

\[N\text{-(2-Nitrophenyl)methylidene]aniline (2a).}\] Recrystallized from EtOH to yield yellow powder (9.43 g, 83%). mp: 62-67 °C (lit. 63-64 °C).  
\[N\text{-(4-Nitrophenyl)methylidene]aniline (2b).}\] Recrystallized from EtOAc/hexanes to give bright yellow crystals (8.13 g, 73%). mp: 91-93 °C (lit. 92-93 °C).  
\[N\text{-(3-Nitrophenyl)methylidene]aniline (2c).}\] 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 °C).  
\[N\text{-[4-(Trifluoromethyl)phenyl)methylidene]aniline (2d).}\] Recrystallized from toluene to produce white crystals (4.80 g, 35%). mp: 75-76 °C (lit. 78 °C).  
\[N\text{-[3-(Trifluoromethyl)phenyl)methylidene]aniline (2e).}\] Yellow liquid (lit. mp 47-47.5 °C). This crude material was used for cyclization.  
\[N\text{-(4-Bromophenyl)methylidene]aniline (2f).}\] Recrystallized from toluene to yield white crystals (4.94 g, 38%). mp: 72-73 °C (lit. 72.5-73 °C).  
\[N\text{-(3-Bromophenyl)methylidene]aniline (2g).}\] 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.)  
\[N\text{-[4-Fluorophenyl)methylidene]aniline (2h).}\] Recrystallized from hexanes to give white crystals (6.72 g, 67%). mp: 43-45 °C (lit. 44 °C).  
\[N\text{-[3-Fluorophenyl)methylidene]aniline (2i).}\] Recrystallized from EtOH to produce white crystals (3.99 g, 40%). mp: 33-34 °C (lit. 33-34 °C).  
\[N\text{-[4-Methylphenyl)methylidene]aniline (2k).}\] Recrystallized from hexanes to give pale yellow crystals (9.76 g, 67%). mp: 44-46 °C (lit. 49-51.5 °C).  
\[N\text{-[3-Methylphenyl)methylidene]aniline (2l).}\] Brown liquid (reported as pale brown oil). This crude material was used for cyclization.  
\[N\text{-[4-Methoxyphenyl)methylidene]aniline (2m).}\] Recrystallized from hexanes to give off-white powder (8.99 g, 85%). mp: 61-62 °C (lit. 63 °C).  
\[N\text{-[3-Methoxyphenyl)methylidene]aniline (2n).}\] Orange liquid (reported as oil). 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 Rᵢ previously reported.¹⁹ ¹H NMR (CDCl₃): δ (ppm): 8.25 (1H, d, 3J₇.₃ Hz, Ar connected to C5), 8.10 (1H, d, 3J₇.₃ Hz, Ar connected to C5), 7.63 (2H, m), 7.52 (1H, t, 3J₇.₃ Hz), 7.29 (1H, t, 3J₇.₃ Hz), 7.11 (1H, d, 3J₇.₃ 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): λₘₐₓ: 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 Rᵢ 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, 3J₇.₃ Hz, Ar connected to C5), 8.14 (2H, d, 3J₇.₃ Hz), 7.63 (2H, d, 3J₇.₃ Hz), 7.42 (2H, m), 7.38 (1H, td, 3J₇.₃ Hz, 4J₇.₃ Hz), 7.33 (3H, d, 3J₇.₃ Hz), 7.31 (1H, m), 7.19 (1H, dd, 3J₇.₃ Hz, 4J₇.₃ 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, 127.0, 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): λₘₐₓ: 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 Rᵢ previously reported.¹⁷ ¹H NMR (CDCl₃): δ (ppm): 8.36 (1H, s), 8.24 (1H, d, 3J₇.₃ Hz, Ar connected to C5), 8.12 (1H, d, 3J₇.₃ Hz), 7.79 (1H, d, 3J₇.₃ Hz), 7.49-7.29 (8H, m), 7.20 (1H, d, 3J₇.₃ 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. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) (ppm): 8.24 (1H, d, \( 3^J_{HH} \) 7.3 Hz, Ar connected to C5), 7.57 (4H, t, \( 3^J_{HH} \) 8.5 Hz), 7.43-7.29 (7H, m, 7.19 (1H, d, \( 3^J_{HH} \) 8.5 Hz), 6.08 (1H, s, C2). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) (ppm): 163.6 (C=O), 143.7, 142.3, 132.7, 132.6, 130.5, 130.4 (q, \( 2^J_{CF} \) 32.6 Hz, Ar C connected to CF3), 129.4, 127.5, 127.6, 126.8, 125.8, 126.4, 125.7, 125.5 (q, \( 3^J_{CF} \) 3.7 Hz, Ar ortho to CF3), 1243.8 (q, \( 1^J_{CF} \) 271.7 Hz, CF3), 64.8 (C2). HRMS (m/z): [M+H]^+ of 386.0814 is consistent with calculated [M+H]^+ of 386.0821. IR (neat, cm\(^{-1}\)): 1651 (s, C=O). UV/Vis (CH\(_3\)CN): \( \lambda_{max} \): 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, 0.495 g. Recrystallization from cyclohexane gave white flakes, 0.28 g (12%), mp: 114-115 °C. \( R_f \) (25% EtOAc/hexanes): 0.50. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) (ppm): 8.23 (1H, d, \( 3^J_{HH} \) 7.6 Hz, Ar connected to C5), 7.71 (1H, s), 7.63 (1H, d, \( 3^J_{HH} \) 7.3 Hz), 7.51 (1H, d, \( 3^J_{HH} \) 7.3 Hz), 7.41-7.29 (8H, m), 7.20 (1H, d, \( 3^J_{HH} \) 7.6 Hz), 6.10 (1H, s, C2). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) (ppm): 163.6, 142.3, 140.7, 132.7, 131.42-130.64 (q, \( 2^J_{CF} \) 32.7 Hz, Ar C connected to CF3), 130.5, 129.7; 129.43, 129.41, 129.0, 127.8, 127.5, 126.8, 125.8, 125.24-125.15 (q, \( 2^J_{CF} \) 3.5 Hz), 123.55-123.46 (q, \( 3^J_{CF} \) 4.0 Hz, Ar ortho to CF3); 127.0, 124.8, 122.6, and 120.5 (q, \( 1^J_{CF} \) 272.7 Hz, CF3, Ar ortho to CF3); 64.9 (C2), 26.9. HRMS (m/z): [M+H]^+ of 386.0817 is consistent with calculated [M+H]^+ of 386.0821. IR (neat, cm\(^{-1}\)): 1649 (s, C=O). UV/Vis (CH\(_3\)CN): \( \lambda_{max} \): 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. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) (ppm): 8.22 (1H, d, \( 3^J_{HH} \) 7.3 Hz, Ar connected to C5), 7.40 (4H, t, \( 3^J_{HH} \) 7.9 Hz), 7.37-7.27 (7H, m, 7.19 (1H, d, \( 3^J_{HH} \) 8.5 Hz), 6.01 (1H, s, C2). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) (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): [M+H]^+ of 396.0049 for \(^{79}\)Br is consistent with calculated [M+H]^+ of 396.0052 and [M+H]^+ of 398.0032 for \(^{81}\)Br is consistent with calculated [M+H]^+ of 398.0032. IR (neat, cm\(^{-1}\)): 1646 (s, C=O). UV/Vis (CH\(_3\)CN): \( \lambda_{max} \): 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. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) (ppm): 8.23 (1H, d, \( 3^J_{HH} \) 9.8 Hz, Ar connected to C5), 7.60 (1H, s), 7.42-7.28 (9H, m), 7.20 (1H, d, \( 3^J_{HH} \) 7.3 Hz), 7.15 (1H, m), 6.01 (1H, s, C2). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) (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): [M+H]^+ of 396.0051 for \(^{79}\)Br is consistent with calculated [M+H]^+ of 396.0052 and [M+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. Rf (30% EtOAc/hexanes): 0.54. 1H NMR (CDCl₃): δ (ppm): 8.23 (1H, d, 3JHH 8.1 Hz, Ar connected to C5), 7.43-7.27 (9H, m), 7.20 (1H, d, 3JHH 7.7 Hz), 6.96 (2H, triplet, 3JHH 3JHE 8.3 Hz), 6.06 (1H, s, C2). 13C NMR (CDCl₃): δ (ppm): 163.7 (C=O); 163.26 and 161.62 (d, 1JCF 248.5 Hz, C-F); 142.3, 135.23 and 135.21 (d, 4JCF 3.3 Hz Ar para to CF); 133.1, 132.5, 130.5, 129.4, 124.3, 128.44 and 128.38 (d, 3JCF 8.8 Hz Ar meta to CF); 127.7, 127.3, 126.5, 125.8; 115.54 and 115.39 (d, 2JCF 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. Rf (20% EtOAc/hexanes): 0.33. 1H NMR (CDCl₃): δ (ppm): 8.23 (1H, dd, 3JHH 7.8, 4JHH 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, 1JCF 248 Hz, C-F); 163.6 (C=O); 142.4; 142.29 and 142.24 (d, 3JCF 7.3 Hz, Ar meta to CF); 135.7, 130.5; 130.03 and 129.97 (d, 1JCF 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, 4JCF 2.8 Hz, Ar para to CF); 115.48 and 115.32 (d, 2JCF 20.9 Hz Ar ortho to CF); 114.00 and 113.81 (d, 2JCF 23.6 Hz, Ar ortho to CF); 64.8 (d, 4JCF 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): λmax: 275 nm (shoulder at approx. 314 nm).

2,3-Diphenyl-2,3-dihydro-4H-1,3-benzothiazin-4-one (1j). All data previously reported. New measurements of UV-Visible spectrum: λmax (CH₃CN): 272 (shoulder at approx. 308 nm) 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. Rf (20% EtOAc/hexanes): 0.34. 1H NMR (CDCl₃): δ (ppm): 8.24 (1H, d, 3JHH 8.1 Hz, Ar connected to C5), 7.39-7.25 (10H, m), 7.18 (1H, d, 3JHH 7.7 Hz), 7.08 (1H, d, 3JHH 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): λmax: 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. Rf (15% EtOAc/hexanes): 0.25. 1H NMR (CDCl₃): δ (ppm): 8.24 (1H, d, 3JHH 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, $^3J_{HH}$ 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): [M+H]$^+$ of 332.1098 is consistent with calculated [M+H]$^+$ of 332.1104. IR (neat, cm$^{-1}$): 1648 (s, C=O). UV/Vis (CH3CN): $\lambda_{\text{max}}$: 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. $^1$H NMR (CDCl3): δ (ppm): 8.23 (1H, dd, $^3J_{HH}$ 8.1, $^4J_{HH}$ 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): [M+H]$^+$ of 348.1046 is consistent with calculated [M+H]$^+$ of 348.1053. IR (neat, cm$^{-1}$): 1645 (s, C=O). UV/Vis (CH3CN): $\lambda_{\text{max}}$: 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. $^1$H NMR (CDCl3): δ (ppm): 8.23 (1H dd, $^3J_{HH}$ 7.9, $^4J_{HH}$ 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, $^3J_{HH}$ 8.3 Hz, $^4J_{HH}$ 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): [M+H]$^+$ of 348.1045 is consistent with calculated [M+H]$^+$ of 348.1053. IR (neat, cm$^{-1}$): 1653 (s, C=O). UV/Vis (CH3CN): $\lambda_{\text{max}}$: 278 nm (shoulder at approx. 314 nm).

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**Supplementary Material**

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

   http://dx.doi.org/10.6023/cjoc201412053

   http://dx.doi.org/10.1016/j.carres.2016.02.011

   http://dx.doi.org/10.1016/j.ejmech.2012.02.007

   http://dx.doi.org/10.1021/acs.jmedchem.5b00910

   http://dx.doi.org/10.1016/j.ejmech.2009.10.044

   http://dx.doi.org/10.1002/jhet.2429

   http://dx.doi.org/10.1021/jm300887b

   http://dx.doi.org/10.1002/jhet.1886

   http://dx.doi.org/10.1016/j.bmc.2009.06.056


    http://dx.doi.org/10.1016/j.cbpa.2010.02.018

    http://dx.doi.org/10.6023/cjoc201603034

    http://dx.doi.org/10.5539/ijc.v7n2p150

    http://dx.doi.org/10.1080/10426509808035677


29. Müller, K.; Faeh, C.; Diederich, F. *Science*, 2007, 317 (5486), 1881-1886. [http://dx.doi.org/10.1126/science.1131943](http://dx.doi.org/10.1126/science.1131943)


44. Maginnity, P. M.; Eisenmann, J. L. *J. Am. Chem. Soc.* **1952**, *74*, 6119-6121. [http://dx.doi.org/10.1021/ja01143a518](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](http://dx.doi.org/10.1021/ja01508a023)


http://dx.doi.org/10.1021/jm101115u