A convenient modified synthesis of 5-pyridinyl-1,3,4-thiadiazole-2-carboxamides

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Dedicated to Prof. Oleg Rakitin on the occasion of his 65th birthday

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Abstract

A general one-pot procedure is developed for the synthesis of 5-pyridinyl-1,3,4-thiadiazole-2-carboxamides by the reaction of pyridine carboxaldehydes with oxamic acid thiohydrazides.

Keywords: Pyridine carboxaldehydes, 1,3,4-thiadiazoles, oxamic acid thiohydrazides, pyridinyl thiadiazoles, carboxamides
Introduction

1,3,4-Thiadiazoles possess a broad spectrum of biological activities.\(^1\) Pyridinyl-1,3,4-thiadiazolecarboxamides, in particular, are of great interest. The latter compounds have attracted attention as insecticides,\(^5\) inhibitors of the type III secretion system of pathogenic bacteria,\(^6\) and cysteine protease inhibitors.\(^7\) This encouraged us to develop a facile synthesis of 5-pyridin-2,3 or 4-yl-1,3,4-thiadiazole-2-carboxamides.

The main multistep method for the synthesis of 5-pyridinyl-1,3,4-thiadiazolecarboxamides involves the acylation of pyridine carbohydrazides with ethyl chlorooxoacetate, the cyclization to the thiadiazole ring, the saponification of the ester group to the carboxyl one, the activation of the latter and the reaction with amines\(^5,7\) (as described for the pyridin-4-yl isomer in Scheme 1). However, the synthesis of 5-pyridin-2-yl-1,3,4-thiadiazolecarboxamides was not described by this method.

Scheme 1. Synthesis of 5-pyridin-4-yl-1,3,4-thiadiazolecarboxamides.

In this work, we report a new general procedure for the synthesis of 1,3,4-thiadiazole-2-carboxamides substituted at the 5-position by a pyridin-2,3, or 4-yl group.

Results and Discussion

One of the known methods reported for the synthesis of 1,3,4-thiadiazoles is based on the oxidation of thiohydrazones produced by the reaction of thiohydrazides with aldehydes.\(^8\)

Scheme 2. Synthesis of thiadiazoles from thiohydrazones.
We have extended this approach to the synthesis of 1,3,4-thiadiazole-2-carboxamides containing a pyridin-2, 3, or 4-yl group at 5-position based on the previously unknown pyridine-containing hydrazones of oxamic acid thiohydrazides 14a-m. The latter compounds 14a-m were synthesized according to Scheme 3 via the reaction of available α-chloroacetamides 12a-m with a previously prepared solution of elemental sulfur and morpholine followed by the addition of hydrazine-hydrate.\(^9\)

\[
\begin{align*}
R-NH_2 & \rightarrow \text{Cl} & \text{N} & \rightarrow \text{Cl} \\
11a-m & \rightarrow 12a-m & 13a-m & \rightarrow 14a-m
\end{align*}
\]

\(R = 3,5(a)/2,4(b)/2,5(c)/3,4(d)/2,6(e)-(\text{MeO})_2\text{C}_6\text{H}_3, 2,4-\text{Cl}_2\text{C}_6\text{H}_3(f), 2-\text{Py}(g), \text{Ph}(h), 4-\text{Br-C}_6\text{H}_4(i), 3-\text{Cl-C}_6\text{H}_4(j), 3-\text{MeO-C}_6\text{H}_4(k), 2,6-(\text{CH}_3)_2\text{C}_6\text{H}_4(l), 2-\text{CH}_3\text{C}_6\text{H}_4(m)\)

**Scheme 3.** Synthesis of oxamic acid thiohydrazides.

We investigated the effect of solvents, catalysts, and temperature on the yield of thiadiazole 18g produced by the reaction of 4-pyridine carboxaldehyde 15c with available oxamic acid N-phenyl-2-thiohydrazide 14h. It was found that the reaction performed in different solvents (Table 1) does not stop at the formation of hydrazone 16g or the equilibrium tautomer form dihydrothiadiazole 17g, but immediately gives thiadiazole 18g after auto-oxidation step with air oxygen (Scheme 4). In inert atmosphere the performed reaction does not lead to unoxidized compound (hydrazone 16g or dihydrothiadiazole 17g).

**Table 1.** Effect of solvents on the yield of thiadiazole 18g

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>-</td>
</tr>
<tr>
<td>MeCN</td>
<td>60%</td>
</tr>
<tr>
<td>THF</td>
<td>30%</td>
</tr>
<tr>
<td>MeOH</td>
<td>80%</td>
</tr>
<tr>
<td>EtOH</td>
<td>80%</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\text{H}_2\text{N} & \rightarrow \text{N} & \rightarrow \text{N} \\
15a: 2-\text{Py} & \rightarrow 16a-r & 17a-r & \rightarrow 18a-r
\end{align*}
\]

**Scheme 4.** Reaction of pyridine carboxaldehydes 15a-c with thiohydrazides 14a-m.
The difference between this reaction and the reaction of oxamic acid thiohydrazides with benzaldehydes described in our previous studies\textsuperscript{10-12} lies in the fact that the latter reaction produces stable hydrazones, which can be transformed into thiadiazoles only after an additional oxidation step. Apparently, the electron-withdrawing nature of pyridine facilitates the formation of the dihydrothiazole moiety followed by oxidation to the thia diazole ring. Therefore, the one-pot reaction of pyridine carboxaldehyde with oxamic acid thiohydrazide involves the formation of hydrazone, its cyclization to the dihydrothiazole moiety, and oxidation to the fully unsaturated thia diazole ring with atmospheric oxygen. The best yields of 18g (80\%) were achieved by refluxing pyridine carboxaldehyde with oxamic acid thiohydrazide in methanol or ethanol.

The use of different acids (acetic, sulfuric, \textit{p}-toluenesulfonic acids) as catalysts in the reaction in alcohols did not lead to either an increase in the rate of the formation of thia diazole or a higher yield of product.

This is a general method, which can be applied to perform the reactions with three isomers of pyridine carboxaldehyde and prepare thia diazoles containing different substituents in the car bamoyl moiety 18a-r. The yields of thia diazoles are given in Table 2. The reaction was performed in ethanol for 12–24 h. The completion of the reaction was monitored by TLC.

\textbf{Table 2. Yield of thia diazoles 18a-r}

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Pyridinyl group</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18a</td>
<td>2,4-Cl\textsubscript{2}C\textsubscript{6}H\textsubscript{3}</td>
<td>4-Py</td>
<td>12</td>
<td>80</td>
</tr>
<tr>
<td>18b</td>
<td>2,6-(MeO)\textsubscript{2}C\textsubscript{6}H\textsubscript{3}</td>
<td>3-Py</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>18c</td>
<td>2,4-(MeO)\textsubscript{2}C\textsubscript{6}H\textsubscript{3}</td>
<td>2-Py</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>18d</td>
<td>2,4-Cl\textsubscript{2}C\textsubscript{6}H\textsubscript{3}</td>
<td>3-Py</td>
<td>12</td>
<td>85</td>
</tr>
<tr>
<td>18e</td>
<td>4-BrC\textsubscript{6}H\textsubscript{4}</td>
<td>4-Py</td>
<td>12</td>
<td>74</td>
</tr>
<tr>
<td>18f</td>
<td>2-CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}</td>
<td>4-Py</td>
<td>12</td>
<td>44</td>
</tr>
<tr>
<td>18g</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>4-Py</td>
<td>12</td>
<td>80</td>
</tr>
<tr>
<td>18h</td>
<td>Ph</td>
<td>3-Py</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>18i</td>
<td>2-Py</td>
<td>3-Py</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>18j</td>
<td>3,5-(MeO)\textsubscript{2}C\textsubscript{6}H\textsubscript{3}</td>
<td>4-Py</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td>18k</td>
<td>2-Py</td>
<td>4-Py</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>18l</td>
<td>3-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>4-Py</td>
<td>12</td>
<td>75</td>
</tr>
<tr>
<td>18m</td>
<td>3-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>4-Py</td>
<td>12</td>
<td>56</td>
</tr>
<tr>
<td>18n</td>
<td>3-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>3-Py</td>
<td>12</td>
<td>54</td>
</tr>
<tr>
<td>18o</td>
<td>3-FC\textsubscript{6}H\textsubscript{4}</td>
<td>3-Py</td>
<td>12</td>
<td>69</td>
</tr>
<tr>
<td>18p</td>
<td>2,5-(MeO)\textsubscript{2}C\textsubscript{6}H\textsubscript{3}</td>
<td>3-Py</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>18q</td>
<td>2,5-(MeO)\textsubscript{2}C\textsubscript{6}H\textsubscript{3}</td>
<td>4-Py</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>18r</td>
<td>2,6-(MeO)\textsubscript{2}C\textsubscript{6}H\textsubscript{3}</td>
<td>4-Py</td>
<td>12</td>
<td>40</td>
</tr>
</tbody>
</table>

As can be seen in Table 2, the nature of oxamic acid thiohydrazides has no significant effect on the reaction rate. The rate of the formation of thia diazole 18c from the 2-pyridinyl isomer is lower than that from the other two isomers due apparently to the slower oxidation step. The formation of 5-pyridin-2-yl-1,3,4-thia diazolecarboxamide 18c is accelerated by bubbling air, which facilitates the oxidation of intermediate dihydrothia diazole 17c.
Conclusions

A convenient general one-pot method with auto-oxidation step for the synthesis of pyridinyl-1,3,4-thiadiazole-2-carboxamides was developed based on the reaction of pyridine carboxaldehydes (2, 3, or 4 isomers) with the readily available oxamic acid hydrazides. This method allows the synthesis of 1,3,4-thiadiazoles containing different substituents at the 5-position, including the three isomers of pyridyl substituents, without isolation of the hydrazone intermediates.

Experimental Section

General. The $^1$H NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer in CDCl$_3$ and DMSO-$d_6$. $^{13}$C NMR spectra, on a Bruker AM-300 (75 MHz) spectrometer in CDCl$_3$ and DMSO-$d_6$; residual protons and the carbon atom of the solvent were used as the internal standard. Elemental analysis was performed on a Merck Silica gel 60 F254 UV-254 plates.

 α-Chloroacetamides 12a-m were prepared by a standard procedure from chloroacetyl chloride and appropriate amines in dichloromethane.

The synthesis of thiohydrazides 14g-m was described previously; oxamic acid thiohydrazides 14a-f were synthesized by procedures described in the cited references.

$N$-(3,5-Dimethoxyphenyl)-2-hydrazinyl-2-thioxoacetamide (14a). Pale yellow crystals (47%); m.p. 115 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.13 (s, 1H, NH), 7.06 (s, 2H, Ar), 6.84 (s, 1H, NH$_2$), 6.31 (s, 1H, NH$_2$), 3.74 (s, 6H, Me). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 165.5 (C=S), 157.8 (C=O), 154.5, 144.7, 126.6, 121.9, 107.1, 104.2, 57.7 (1C, CH$_3$), 56.0 (2C, CH$_3$), C. 47.05; H, 5.13; N, 16.46. Found: C, 47.22; H, 5.20; N, 16.21 %. MS (EI): m/z (%) 255 (M$^+$+H, 55), 153 (C$_6$H$_5$NO$_2$$^+$, 100).

$N$-(2,4-Dimethoxyphenyl)-2-hydrazinyl-2-thioxoacetamide (14b). Pale yellow crystals (80%); m.p. 150 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.24 (s, 1H), 8.15 (d, $J$ = 8.5 Hz, 1H), 7.95 (s, 1H), 6.70 (s, 1H), 6.57 (dd, $J$ = 9.5, 1.1 Hz, 1H), 4.97 (s, 1H), 3.90 (s, 3H), 3.76 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 166.5(C=S), 158.9(C=O), 153.5, 148.5, 123.6, 112.8, 108.7, 104.1, 56.0(1C, CH$_3$), 55.7 (1C, CH$_3$). Calcd for C$_{10}$H$_7$N$_3$O$_5$S: C, 47.05; H, 5.13; N, 16.46. Found: C, 47.22; H, 5.20; N, 16.21 %. MS (EI): m/z (%) 255 (M$^+$+H, 64), 153 (C$_6$H$_7$NO$_2$$^+$, 100).

$N$-(2,5-Dimethoxyphenyl)-2-hydrazinyl-2-thioxoacetamide (14c). Pale yellow crystals (77%); m.p. 120 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.44 (s, 1H), 7.94 (d, $J$ = 3.1 Hz, 1H), 7.04 (d, $J$ = 9.0 Hz, 1H), 6.77-6.65 (m, 1H), 3.86 (s, 3H), 3.71 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 168.5 (C=S), 157.8 (C=O), 153.5, 142.7, 127.6, 111.9, 108.1, 106.3, 56.7 (1C, CH$_3$), 55.7 (1C, CH$_3$). Calcd for C$_{10}$H$_7$N$_3$O$_5$S: C, 47.05; H, 5.13; N, 16.46. Found: C, 47.18; H, 5.19; N, 16.51 %. MS (EI): m/z (%) 255 (M$^+$+H, 50), 153 (C$_6$H$_7$NO$_2$$^+$, 100).

$N$-(3,4-Dimethoxyphenyl)-2-hydrazinyl-2-thioxoacetamide (14d). Pale yellow crystals (77%); m.p. 135 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.07 (s, 1H, NH), 9.04 (s, 1H, NH$_2$), 7.95 (s, 1H, NH$_2$), 7.41
(d, J = 1.9 Hz, 1H, Ar), 7.30 (s, 1H, Ar), 6.89 (m, 1H, Ar), 5.86 (s, 1H, NH$_2$), 2.89 (s, 3H, CH$_3$), 2.73 (s, 3H, CH$_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 166.4 (C=O), 156.8 (C=O), 154.5, 145.7, 127.6, 111.9, 110.1, 105.4, 57.7 (1C, CH$_3$), 56.2 (1C, CH$_3$). Calcd for C$_{10}$H$_{12}$N$_2$O$_3$: C, 316-325. H NMR (300 MHz, CDCl$_3$) δ 169.4 (C=O), 156.4 (C=O), 152.3 (1C, Py), 148.8 (1C, Py), 135.2 (1C, Py), 128.5 (2C, Ar), 126.1 (1C, Py), 124.0 (1C, Ar), 123.4 (1C, Py), 112.5 (1C, Ar), 104.3 (2C, Ar), 56.0 (2C, CH$_3$). HRMS (ESI) C$_{16}$H$_{14}$N$_2$O$_3$S. Calcd for (M+H)$^+$: 350.9869. Found: 350.9865.

**N-(2,6-Dimethoxyphenyl)-5-(pyridin-4-yl)-1,3,4-thiadiazole-2-carboxamide (18b).** Colorless crystals (50%); m.p. 170 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 9.25 (s, 1H, NH$_2$), 8.81 (d, J = 4.4 Hz, 1H, Py), 8.58 (s, 1H, Py), 8.38 (d, J = 7.9 Hz, 1H, Py), 7.51 (dd, J = 7.7, 5.0 Hz, 1H, Ar), 7.31 (dd, J = 7.7, 5.0 Hz, 1H, Ar), 6.67 (d, J = 8.4 Hz, 2H, Ar), 3.89 (s, 6H, CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.4 (C, thiadiazole), 165.69 (1C, C=O), 155.4 (C, thiadiazole), 152.3 (1C, Py), 148.8 (1C, Py), 135.2 (1C, Py), 128.5 (2C, Ar), 126.1 (1C, Py), 124.0 (1C, Ar), 123.4 (1C, Py), 112.5 (1C, Ar), 104.3 (2C, Ar), 56.0 (2C, CH$_3$). HRMS (ESI) C$_{16}$H$_{14}$N$_2$O$_3$S. Calcd for (M+H)$^+$: 343.0859. Found: 343.0858.

**N-(2,4-Dimethoxyphenyl)-5-(pyridin-2-yl)-1,3,4-thiadiazole-2-carboxamide (18c).** Yellow crystals (50%); m.p. 170 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 9.62 (s, 1H, NH$_2$), 8.38 (d, J = 7.9 Hz, 1H, Py), 7.51 (dd, J = 7.7, 5.0 Hz, 1H, Ar), 7.31 (dd, J = 7.7, 5.0 Hz, 1H, Ar), 6.67 (d, J = 8.4 Hz, 2H, Ar), 3.89 (s, 6H, CH$_3$). $^{13}$C NMR (75 MHz, DMSO-$d_6$) low solubility. HRMS (ESI)
C_{16}H_{14}N_{4}O_{3}S. Calcd for (M+H)^+: 343.0859. Found: 343.0854.

**N-(2,4-Dichlorophenyl)-5-(pyridin-3-yl)-1,3,4-thiadiazole-2-carboxamide (18d).** Colorless crystals (85%); m.p. 205 °C. ^1^H NMR (300 MHz, CDCl_3) δ 9.26 (s, 1H, NH), 9.15 (s, 1H, Py), 8.83 (m, 1H, Py), 8.38 (d, J = 7.0 Hz, 1H, Py), 8.01 (s, 1H, Ar), 7.61–7.46 (m, 3H, Ar+Py). ^13^C NMR (75 MHz, DMSO-d_6) δ 170.0 (C, thiadiazole), 167.2 (1C, C=O), 166.9 (C, thiadiazole), 156.0 (1C, Py), 152.2 (1C, Py), 148.1 (1C, Py), 136.2 (1C, Ar), 137.2 (1C, Py), 131.4 (1C, Ar), 130.1 (1C, Py), 125.9 (1C, Ar), 123.2 (1C, Ar), 122.1 (1C, Ar), 120.2 (1C, Ar). HRMS (ESI) C_{14}H_{10}Cl_{2}N_{4}OS. Calcd for (M+H)^+: 350.9869. Found: 350.9865.

**N-(4-Bromophenyl)-5-(pyridin-4-yl)-1,3,4-thiadiazole-2-carboxamide (18e).** Colorless crystals (74%); m.p. 235 °C. ^1^H NMR (300 MHz, CDCl_3) δ 9.15 (s, 1H, NH), 8.87 (d, J = 5.5 Hz, 2H, Py), 7.92 (d, J = 5.6 Hz, 2H, Py), 7.63 (d, J = 8.8 Hz, 2H, Ar), 7.56 (d, J = 8.8 Hz, 2H, Ar). ^13^C NMR (75 MHz, DMSO-d_6) δ 170.4 (C, thiadiazole), 167.2 (1C, C=O), 156.4 (C, thiadiazole), 151.4 (2C, Py), 137.4 (1C, Py), 136.3 (1C, Ar), 132.1 (2C, Py), 123.2 (2C, Ar), 122.20 (2C, Ar), 117.25 (1C, Ar). HRMS (ESI) C_{14}H_{9}BrN_{4}OS.

Calcd for (M+H)^+: 360.9753. Found: 360.9743.

**5-(Pyridin-4-yl)-N-(o-tolyl)-1,3,4-thiadiazole-2-carboxamide (18f).** Colorless crystals (44%); m.p. 160 °C. ^1^H NMR (300 MHz, CDCl_3) δ 9.12 (s, 1H, NH), 8.86 (d, J = 5.7 Hz, 2H, Py), 8.12 (d, J = 8.0 Hz, 1H, Ar), 7.91 (d, J = 5.9 Hz, 2H, Py), 7.33 (d, J = 7.7 Hz, 1H, Ar), 7.19 (t, J = 7.4 Hz, 1H, Ar), 2.45 (s, 3H, CH_3). ^13^C NMR (75 MHz, DMSO-d_6) δ 156.4 (1C, C=O), 151.4 (C, thiadiazole), 151.0 (C, thiadiazole), 136.4 (2C, Py), 135.2 (2C, Py), 134.0 (1C, Ar), 130.9 (1C, Py), 127.2 (1C, Ar), 126.8 (1C, Ar), 126.6 (1C, Ar), 123.1 (1C, Ar), 122.2 (1C, Ar), 18.49 (1C, CH_3). HRMS (ESI) C_{15}H_{12}N_{4}OS. Calcd for (M+H)^+: 297.0805. Found: 290.0801.

**N-Phenyl-5-(pyridin-4-yl)-1,3,4-thiadiazole-2-carboxamide (18g).** White crystals (80%); m.p. 210-212 °C. ^1^H NMR (300 MHz, DMSO-d_6) δ 11.28 (s, 1H, NH), 8.83 (d, J = 5.6 Hz, 2H, Py), 8.05 (d, J = 5.7 Hz, 2H, Py), 7.87 (d, J = 7.9 Hz, 2H, Ar), 7.40 (t, J = 7.8 Hz, 2H, Ar), 7.19 (t, J = 7.3 Hz, 1H, Ar). ^13^C NMR (75 MHz, DMSO-d_6) δ 170.3 (C, thiadiazole), 167.4 (1C, C=O), 156.3 (C, thiadiazole), 151.4 (2C, Py), 138.0 (1C, Py), 136.4 (1C, Ar), 129.2 (2C, Py), 125.3 (1C, Ar), 122.1 (2C, Ar), 121.3 (2C, Ar). HRMS (ESI) C_{14}H_{10}N_{4}OS. Calcd for (M+H)^+: 283.0648. Found: 283.0646.

**N-Phenyl-5-(pyridin-3-yl)-1,3,4-thiadiazole-2-carboxamide (18h).** White crystals (60%); m.p. 190-192 °C. ^1^H NMR (300 MHz, DMSO-d_6) δ 11.27 (s, 1H, NH), 9.28 (s, 1H, Py), 8.82 (d, J = 4.8 Hz, 1H, Py), 8.50 (dd, J = 4.4, 3.7 Hz, 1H, Py), 7.88 (d, J = 7.9 Hz, 2H, Ar), 7.66 (dd, J = 7.9, 4.9 Hz, 1H, Py), 7.41 (t, J = 7.8 Hz, 2H, Ar), 7.19 (t, J = 7.2 Hz, 1H, Ar). ^13^C NMR (75 MHz, DMSO-d_6) δ 169.5 (C, thiadiazole), 166.7 (C, thiadiazole), 166.6 (C=O), 156.4 (1C, Py), 152.9 (1C, Py), 148.9 (1C, Py), 138.0 (1C, Py), 135.9 (1C, Ar), 129.2 (1C, Py), 125.2 (2C, Ar), 124.8 (1C, Ar), 121.3 (2C, Ar). HRMS (ESI) C_{14}H_{10}N_{4}OS. Calcd for (M+H)^+: 283.0648. Found: 283.0646.

**N-(Pyridin-2-yl)-5-(pyridin-3-yl)-1,3,4-thiadiazole-2-carboxamide (18i).** White crystals (38%); m.p. 180-182 °C. ^1^H NMR (300 MHz, CDCl_3) δ 9.71 (s, 1H, NH), 9.02 (s, 1H, Py), 8.82 (d, J = 4.1 Hz, 1H, Py), 8.23 (d, J = 8.3 Hz, 1H, Py), 7.92 (d, J = 7.8 Hz, 1H, Py), 7.82 (t, J = 7.4 Hz, 1H, Py), 7.52 (dd, J = 7.8, 4.9 Hz, 1H, Py), 7.39 (dd, J = 7.7, 5.0 Hz, 1H, Py), 7.12–7.03 (m, 1H, Py). ^13^C NMR (75 MHz, CDCl_3) δ 171.9 (C, thiadiazole), 165.8 (C=O), 153.4 (C, thiadiazole), 156.6 (1C, Py), 151.1 (1C, Py), 147.9 (1C, Py), 148.5 (1C, Py),
N-(3,5-Dimethoxyphenyl)-5-(pyridin-4-yl)-1,3,4-thiadiazole-2-carboxamide (18j). Yellow crystals (70%); m.p. 179-180 °C. \(^1^H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.19 (s, 1H, NH), 8.96 (d, \(J = 4.1\) Hz, 2H, Py), 8.06-7.97 (m, 2H, Py), 7.38 (1H, Ar), 7.06 (d, \(J = 2.0\) Hz, 1H, Ar), 6.47 (d, \(J = 1.9\) Hz, 1H, Ar), 3.95 (s, 6H, CH\(_3\)). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) low solubility. HRMS (ESI) C\(_{16}\)H\(_{14}\)N\(_4\)O\(_3\)S. Calcd for (M+H)\(^+\): 343.0859. Found: 343.0850.

N-(Pyridin-2-yl)-5-(pyridin-4-yl)-1,3,4-thiadiazole-2-carboxamide (18k). White crystals (68%); m.p. 190-192 °C. \(^1^H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.73 (s, 1H, NH), 8.86 (d, \(J = 5.3\) Hz, 2H, Py), 8.43 (d, \(J = 4.1\) Hz, 1H, Py), 8.32 (d, \(J = 8.3\) Hz, 1H, Py), 7.92 (d, \(J = 5.3\) Hz, 2H, Py'), 7.82 (t, \(J = 7.8\) Hz, 1H, Py), 7.23-7.13 (m, 1H, Py). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.9 (C, thiadiazole), 165.6 (C=O), 155.4 (C, thiadiazole), 151.1 (2C, Py), 149.9 (1C, Py), 148.5 (1C, Py), 138.5 (2C, Py'), 136.3 (1C, Py), 121.6 (1C, Py), 120.9 (1C, Py), 114.3 (1C, Py). HRMS (ESI) C\(_{13}\)H\(_9\)N\(_5\)O\(_3\). Calcd for (M+H)\(^+\): 284.0601. Found: 284.0601.

N-(3-Chlorophenyl)-5-(pyridin-4-yl)-1,3,4-thiadiazole-2-carboxamide (18l). Colorless crystals (75%); m.p. 175-177 °C. \(^1^H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.16 (s, 1H, NH), 8.86 (d, \(J = 5.8\) Hz, 2H, Py), 7.95 – 7.87 (m, 3H, Py+Ar), 7.56 (d, \(J = 9.1\) Hz, 1H, Py), 7.36 (t, \(J = 8.1\) Hz, 1H, Py), 7.22 (d, \(J = 8.5\) Hz, 1H, Ar). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 165.8 (C=O), 155.0 (C, thiadiazole), 151.1 (2C, Py), 137.4 (C, thiadiazole), 136.2 (2C, Py), 135.0 (1C, Py), 130.3 (1C, Ar), 125.6 (1C, Ar), 121.6 (1C, Ar), 120.1 (1C, Ar), 118.0 (1C, Ar), 115.7 (1C, Ar). HRMS (ESI) C\(_{14}\)H\(_9\)ClN\(_4\)O\(_4\). Calcd for (M+H)\(^+\): 317.0258. Found: 317.0248.

N-(3-Methoxyphenyl)-5-(pyridin-4-yl)-1,3,4-thiadiazole-2-carboxamide (18m). Colorless crystals (56%); m.p. 150-153 °C. \(^1^H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.15 – 9.03 (m, 1H, NH), 8.90 – 8.81 (m, 2H, Py), 7.92 (d, \(J = 6.0\) Hz, 2H, Py), 7.47 (s, 1H, Ar), 7.34 (t, \(J = 8.1\) Hz, 1H, Ar), 7.22 (d, \(J = 7.9\) Hz, 1H, Ar), 6.81 (d, \(J = 7.9\) Hz, 1H, Ar), 3.88 (s, 3H, CH\(_3\)). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) 170.7 (C, thiadiazole), 167.7 (C=O), 166.8 (C, thiadiazole), 152.1 (2C, Py), 148.9 (1C, Py), 139.0 (1C, Ar), 125.9 (2C, Py), 130.0 (1C, Ar), 113.6 (1C, Ar), 110.9 (1C, Ar), 106.2 (1C, Ar), 104.2 (1C, Ar), 57.5 (CH3). HRMS (ESI) C\(_{15}\)H\(_{12}\)N\(_4\)O\(_2\)S. Calcd for (M+H)\(^+\): 313.0754. Found: 313.0762.

N-(3-Methoxyphenyl)-5-(pyridin-3-yl)-1,3,4-thiadiazole-2-carboxamide (18n). Colorless crystals (54%); m.p. 145-147 °C. \(^1^H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.26 (s, 1H, NH), 9.10 (m, 2H, Py), 8.82 (d, \(J = 3.8\) Hz, 1H, Py), 8.38 (d, \(J = 7.8\) Hz, 1H, Py), 7.47 (s, 1H, Ar), 7.34 (t, \(J = 8.2\) Hz, 1H, Ar), 7.22 (d, \(J = 7.9\) Hz, 1H, Ar), 6.80 (d, \(J = 8.2\) Hz, 1H, Ar), 3.88 (s, 3H, CH\(_3\)). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) 169.7 (C, thiadiazole), 166.7 (C=O), 159.8 (C, thiadiazole), 156.1 (1C, Py), 153.0 (1C, Py), 148.9 (1C, Py), 139.0 (1C, Ar), 135.9 (1C, Py), 130.0 (1C, Ar), 124.8 (1C, Py), 113.6 (1C, Ar), 110.9 (1C, Ar), 107.2 (1C, Ar), 105.5 (1C, Ar), 55.5 (CH\(_3\)). HRMS (ESI) C\(_{15}\)H\(_{12}\)N\(_4\)O\(_2\)S. Calcd for (M+H)\(^+\): 313.0754. Found: 313.0762.

N-(4-Fluorophenyl)-5-(pyridin-3-yl)-1,3,4-thiadiazole-2-carboxamide (18o). Colorless crystals (69%); m.p. 200-202 °C. \(^1^H\) NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) 11.35 (s, 1H, NH), 9.27 (s, 1H, Py), 8.81 (d, \(J = 4.0\) Hz, 1H, Py), 8.49 (d, \(J = 7.9\) Hz, 1H, Py), 7.92-7.8 (m, 2H, Ar), 7.72 – 7.58 (m, 1H, Py), 7.31-7.25 (m, 2H, Ar). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) 169.6 (C, thiadiazole), 166.6 (C=O), 160.9 (C, thiadiazole), 156.4 (1C, Py), 153.0 (1C, Py), 148.9 (1C, Py), 135.9 (1C, Py), 124.9 (1C, Py), 123.3 (2C, Ar), 123.2 (1C,
Ar), 116.0 (2C, Ar), 115.7 (1C, Ar). HRMS (ESI) C_{14}H_{9}F_{4}NO. Calcd for (M+H)^+: 301.0554. Found: 301.0550.

**N-(2,5-Dimethoxyphenyl)-5-(pyridin-3-yl)-1,3,4-thiadiazole-2-carboxamide (18p).** Yellow crystals (40%); m.p. 199-200 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.83 (s, 1H, NH), 9.27 (s, 1H, Py), 8.82 (d, $J = 4.7$ Hz, 1H, Py), 8.38 (d, $J = 8.0$ Hz, 1H, Ar), 8.19 (d, $J = 2.7$ Hz, 1H, Py), 7.60-7.48 (m, 1H, Py), 6.90 (d, $J = 8.9$ Hz, 1H, Ar), 6.71 (d, $J = 9.0$ Hz, 1H, Ar), 3.95 (s, 3H, CH$_3$), 3.85 (s, 3H, CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.4 (C, thiadiazole), 165.69 (C, thiadiazole), 155.4 (1C, C=O), 153.5 (1C, Ar), 152.3 (1C, Py), 148.8 (1C, Py), 142.7 (1C, Ar), 135.2 (1C, Py), 128.5 (1C, Py), 126.1 (1C, Py), 128.0 (1C, Ar), 112.4 (1C, Ar), 110.5 (1C, Ar), 104.3 (1C, Ar), 56.0 (1C, CH$_3$), 55.7 (1C, CH$_3$). HRMS (ESI) C$_{16}$H$_{14}$N$_4$O$_3$S. Calcd for (M+H)$^+$: 343.0859. Found: 343.0852.

**N-(2,5-Dimethoxyphenyl)-5-(pyridin-4-yl)-1,3,4-thiadiazole-2-carboxamide (18q).** Orange crystals (40%); m.p. 220-222 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.63 (s, 1H, NH), 8.85 (d, $J = 4.7$ Hz, 2H, Py), 8.37 (d, $J = 8.9$ Hz, 1H, Ar), 7.93 (d, $J = 4.5$ Hz, 2H, Py), 6.60-6.52 (m, 2H, Ar), 3.96 (s, 3H, CH$_3$), 3.86 (s, 3H, CH$_3$). $^{13}$C NMR (75 MHz, DMSO-d$_6$) low solubility. HRMS (ESI) C$_{16}$H$_{14}$N$_4$O$_3$S. Calcd for (M+H)$^+$: 343.0859. Found: 343.0854.

**N-(2,6-Dimethoxyphenyl)-5-(pyridin-4-yl)-1,3,4-thiadiazole-2-carboxamide (18r).** Yellow crystals (40%); m.p. 190-192 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.85 (d, $J = 5.8$ Hz, 2H, Py), 7.91 (d, $J = 5.8$ Hz, 2H, Py), 7.32 (m, 1H, Ar), 6.69 (s, 1H, Ar), 6.66 (s, 1H, Ar), 3.89 (s, 6H, CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.0 (C, thiadiazole), 166.8 (C, thiadiazole), 160.7 (C=O), 152.1 (2C, Py), 148.9 (1C, Py), 150.0 (2C, Ar), 125.9 (2C, Py), 113.6 (1C, Ar), 111.0 (2C, Ar), 104.1 (1C, Ar), 57.5 (2C, CH$_3$). HRMS (ESI) C$_{16}$H$_{14}$N$_4$O$_3$S. Calcd for (M+H)$^+$: 343.0859. Found: 343.0850.

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