Synthesis and evaluation of new 2-aminothiophenes against Mycobacterium tuberculosis

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$^{13}$C-NMR of compound 2-amino-$N$-(2-methoxybenzyl)-4,5,6,7-tetrahydrobenzo$[b]$thiophene-3-carboxamide (52)

$^1$H-NMR of compound $N$-(adamantan-1-yl)-2-amino-4,5,6,7-tetrahydrobenzo$[b]$thiophene-3-carboxamide (53)

$^{13}$C-NMR of compound $N$-(adamantan-1-yl)-2-amino-4,5,6,7-tetrahydrobenzo$[b]$thiophene-3-carboxamide (53)

$^1$H-NMR of compound 2-Amino-$N$-butyl-5-phenylthiophene-3-carboxamide (59)$^{14}$

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$^{13}$C-NMR of compound 2-amino-$N$-benzyl-5-phenylthiophene-3-carboxamide (60)

$^1$H-NMR of compound 2-amino-$N$-(4-methylbenzyl)-5-phenylthiophene-3-carboxamide (61)

$^{13}$C-NMR of compound 2-amino-$N$-(4-methylbenzyl)-5-phenylthiophene-3-carboxamide (61)

$^1$H-NMR of compound 2-Amino-$N$-(2-methoxybenzyl)-5-phenylthiophene-3-carboxamide (62)

$^{13}$C-NMR of compound 2-Amino-$N$-(2-methoxybenzyl)-5-phenylthiophene-3-carboxamide (62)

$^1$H-NMR of compound $N$-(adamantan-1-yl)-2-amino-5-phenylthiophene-3-carboxamide (63)

$^{13}$C-NMR of compound $N$-(adamantan-1-yl)-2-amino-5-phenylthiophene-3-carboxamide (63)
**SI-Figure 1.** HTS of thiophene library against Ag85C

- Average is of the 6 uninhibited reactions.
- ±3σ determined from that average.
- RFU/Min should decrease for inhibition of Ag85C.
- No compounds displayed activity below -3σ.
- -3σ would represent compounds with approximately 25% inhibition.
Experimental for known compounds

6-Benzyl 3-ethyl 2-amino-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (22)¹

![Chemical structure of 6-Benzyl 3-ethyl 2-amino-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (22)]

Yield: 86% (1.36 g); silica gel TLC $R_f = 0.51$ (40% ethyl acetate in hexanes); $^1$H-NMR (600 MHz, CDCl₃): $\delta$ 7.38 (m, 4H, H-19, 20, 22, 23), 7.33 (m, 1H, H-21), 6.02 (s, 2H, H-17), 5.17 (s, 2H, H-8), 4.44 (s, 2H, H-6), 4.26 (q, 2H, 2H, $J_{13,14}$ 6Hz, H-13), 3.71 (s, 2H, H-10), 2.83 (m, 2H, H-5), 1.34 (t, 3H, $J_{14,13}$ 6Hz, H-14); $^{13}$C-NMR (150 MHz, CDCl₃): $\delta$ 165.79 (C-2), 162.34 (C-110, 155.27 (C-15), 136.67 (C-18), 131.66 (C-9), 130 (C-22, 20), 128.10 (C-19,23), 128 (C-21), 113.13 (C-4), 105.22 (C-5), 67.33 (C-17), 56.65 9C-13), 50.92 (C-8), 42.68 (C-6), 41.20 (C-5), 14.45 (C-14); mass spectrum (ESI), $m/z = 383.10$ (M+23)$^+$ C₁₈H₂₀N₂O₄S requires 383.10 (M+23)$^+$.

6-(Tert-butyl) 3-ethyl 2-amino-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (23)²

![Chemical structure of 6-(Tert-butyl) 3-ethyl 2-amino-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (23)]

Yield: 63% (4.2 g); silica gel TLC $R_f = 0.49$ (40% ethyl acetate in hexanes); $^1$H-NMR (600 MHz, CDCl₃): $\delta$ 4.36 (s, 2H, H-9), 4.27 (q, 2H, $J_{16,17}$ 6Hz, H-16), 3.62 (t, 2H, $J_{2,3}$ 6Hz, H-2), 2.81 (t, 2H, $J_{3,2}$ 6Hz, H-3), 1.49 (s, 9H, H-13, 20, 21), 1.35 (t, 3H, $J_{16,17}$ 6Hz, H-17); $^{13}$C-NMR (150 MHz, CDCl₃): $\delta$ 166.54 (C-2), 163.44 (C-11), 153.88 (C-13), 130.80 (C-4, 9), 102.61 (C-3), 79.08 (C-
15), 42.48 (C-8), 41.45 (C-6), 28.07 (C-20, 19, 16), 14.11 (C-5); mass spectrum (ESI), $m/z = 349.1$ (M+23)$^+$ \text{C}_{15}H_{22}N_2O_4S$ requires 349.11 (M+23)$^+$.

**Ethyl 2-amino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (24)$^3$**

![Chemical Structure](image)

Yield: 86% (140.0 mg); silica gel TLC $R_f = 0.2$ (10 % methanol in CH$_2$Cl$_2$); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 5.96 (s, 2H, H-10), 4.25 (q, 2H, $^3$J$_{15,16}$ 7.2 Hz, H-15), 3.43 (s, 2H, H-8), 2.84 (t, 2H, $^3$J$_{5,6}$ 8 Hz, H-5), 2.72 (t, 2H, $^3$J$_{6,5}$ 8 Hz, H-6), 2.58 (q, 2H, $^3$J$_{13,14}$ 7.2 Hz, H-13), 1.33 (t, 3H, $^3$J$_{16,15}$ 7.2 Hz, H-16), 1.17 (t, 3H, $^3$J$_{14,13}$ 7.2 Hz, H-14); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 165.96 (C-2), 162.01 (C-11), 131.14 (C-4), 114.82 (C-9), 105.36 (C-3), 59.41 (C-15), 51.57 (C-12), 51.09 (C-8), 50.23 (C-6), 27.43 (C-5), 14.43 (C-16), 12.58 (C-14); mass spectrum (ESI), $m/z = 277.09$ (M+23)$^+$ \text{C}_{12}H_{18}N_2O_2S$ requires 277.10 (M+23)$^+$.

**Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (25)$^4$**

![Chemical Structure](image)

Yield: 59% (140.0 mg); silica gel TLC $R_f = 0.53$ (10 % ethyl acetate in hexanes); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 5.94 (s, 12H, H-10), 4.26 (q, 2H, $^3$J$_{13,14}$ 7.2 Hz, H-13), 2.71 (t, 2H, $^3$J$_{8,7}$ 5.01 Hz, H-8), 2.51 (t, 2H, $^3$J$_{5,6}$ 5.01 Hz, H-5), 1.80-1.73 (m, 4H, 2 $\times$ CH$_2$, H-6,7), 1.34 (t, 3H, $^3$J$_{14,13}$ 7.2 Hz, H-14); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 166.13 (C-2), 161.63 (C-11), 132.46 (C-4), 117.63 (C-9),
105.76 (C-3), 59.36 (C-13), 26.93 (C-8), 24.52 (C-5), 23.23 (C-7), 22.81 (C-6), 14.46 (C-14); mass spectrum (ESI), \( m/z = 248.07 \) (M+23)+ \( \text{C}_{11}\text{H}_{15}\text{NO}_{2}\text{S} \) requires 248.07 (M+23)+.

**Ethyl 2-amino-5-phenylthiophene-3-carboxylate (26)**

![Chemical structure of Ethyl 2-amino-5-phenylthiophene-3-carboxylate](image)

Yield: 12.5 g, 61% (140.0 mg); silica gel TLC \( R_f = 0.53 \) (30 % ethyl acetate in hexanes); \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.44 (m, 2H, H-12, 16), 7.32 (t, 2H, \( J_{13,14} 6.0 \) Hz, H-13, 15), 7.25 (s, 1H, H-4), 7.21 (s, 1H, H-14), 4.30 (q, 2H, \( J_{9,10} 6 \)Hz H-9), 1.37 (t, 3H, \( J_{10,9} 6 \)Hz H-10); \(^{13}\)C-NMR (150 MHz, CDCl\(_3\)): \( \delta \) 165.54 (C-2), 161.73 (C-7), 129.24 (C-5), 128.97 (C-13, 15, 11), 1226.79 (C-14), 124.89 (C-12, 16), 121.40 (C-3), 60.09 (C-9), 14.72 (C-10); mass spectrum (ESI), \( m/z = 270.05 \) (M+23)+ \( \text{C}_{13}\text{H}_{13}\text{NO}_{2}\text{S} \) requires 270.06 (M+23)+.

**6-(Tert-butyl) 3-ethyl 2-acetamido-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (27)**

![Chemical structure of 6-(Tert-butyl) 3-ethyl 2-acetamido-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate](image)

Yield: 41% (92.6 mg); silica gel TLC \( R_f = 0.67 \) (7 % methanol in CH\(_2\)Cl\(_2\)); \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \( \delta \) 11.25 (s, 1H, H-10), 4.50 (s, 2H, H-8), 4.35 (q, 2H, \( J_{15,16} 7.15 \) Hz, H-15), 3.65 (t, 2H,
$^{3}J_{6,5} 5.67 \text{ Hz, H-6}$, 2.88 (t, $^{3}J_{5,6} 4.97 \text{ Hz, H-5}$), 2.28 (s, 3H, H-21), 1.49 (s, 9H, H-20,24,25), 1.40 (t, 3H, $^{3}J_{15,16} 7.15 \text{ Hz, H-16}$); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 167.11 (C-2), 166.28 (C-11), 154.64 (C-17), 148.44 (C-13), 129.72 (C-4), 123.33 (C-9), 110.82 (C-3), 80.15 (C-19), 60.75 (C-15), 42.63 (C-8), 40.98 (C-6), 26.45 (C-25, 24, 20), 26.55 (C-5), 23.68 (C-21), 14.31 (C-16); mass spectrum (ESI), $m/z = 391.13$ (M+23)$^+$ C$_{17}$H$_{24}$N$_2$O$_5$S requires 391.13 (M+23)$^+$.

**Ethyl 2-acetamido-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (31)**

![Ethyl 2-acetamido-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (31)](image)

Yield: 33% (78.0 mg); silica gel TLC $R_f = 0.30$ (10 % methanol in CH$_2$Cl$_2$); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 11.22 (s, 1H, H-10), 4.34 (q, 2H, $^{3}J_{17,18} 7.15 \text{ Hz, H-17}$), 3.59 (s, 2H, H-8), 2.92 (t, 2H, $^{3}J_{5,6} 5.50 \text{ Hz, H-5}$), 2.79 (t, 2H, H-6), 2.65 (q, 2H, $^{3}J_{15,16} 6.97 \text{ Hz, H-15}$), 2.27 (s, 3H, H-19), 1.38 (t, 3H, $^{3}J_{18,17} 6.97 \text{ Hz, H-18}$), 1.20 (t, 3H, $^{3}J_{16,15} 7.15 \text{ Hz, H-16}$); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 167.13 (C-2), 166.50 (C-11), 148.27 (C-13), 129.39 (C-4), 128.36 (C-9), 110.90 (C-3), 60.72 (C-17), 51.66 (C-15), 51.01 (C-8), 50.24 (C-6), 26.87 (C-5), 23.82 (C-19), 14.43 (C-18), 50.24 (C-6), 26.87 (C-5), 23.82 (C-19), 14.43 (C-18), 12.53 (C-16); mass spectrum (ESI), $m/z = 319.10$ (M+23)$^+$ C$_{14}$H$_{20}$N$_2$O$_3$S requires 319.10 (M+23)$^+$.

**Ethyl 2-acetamido-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxylate (36)**

![Ethyl 2-acetamido-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxylate (36)](image)
Yield: 59% (140.0 mg); silica gel TLC $R_f = 0.41$ (7% methanol in CH$_2$Cl$_2$); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 11.23 (s, 1H, H-10), 4.29 (q, 2H, $^3$J$_{15,16}$ 7.14 Hz, H-15), 2.73 (t, 2H, $^3$J$_{8,7}$ 5.94 Hz, H-8), 2.60 (t, 2H, $^3$J$_{5,6}$ 5.76 Hz, H-5), 2.23 (s, 3H, H-17), 1.78-1.73 (m, 4H, 2 CH$_2$, H-6, 7), 1.36 (t, 3H, $^3$J$_{16,15}$ 7.14, H-16); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 166.88 (C-2), 166.66 (C-11), 147.65 (C-13), 130.65 (C-4), 126.59 (C-9), 111.23 (C-3), 60.46 (C-15), 26.39 (C-8), 24.36 (C-5), 23.74 (C-17), 23.00 (C-7), 22.88 (C-6), 14.34 (C-16); mass spectrum (ESI), $m/z = 290.08$ (M+23)$^+$ C$_{13}$H$_{17}$NO$_3$S requires 290.08 (M+23)$^+$.

**Ethyl-2-benzamido-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (37)$^8$**

![Chemical Structure](image)

Yield: 57.2% (167.0 mg); silica gel TLC $R_f = 0.62$ (7% methanol in CH$_2$Cl$_2$); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 12.32 (s, 1H, H-10), 8.01 (m, 2H, H-18, 22), 7.56 (m, 1H, H-20), 7.50 (m, 2H, H-19, 21), 4.35 (q, 2H, $^3$J$_{15,16}$ 7.14 Hz, H-15), 2.78 (t, 2H, $^3$J$_{8,7}$ 6.0 Hz, H-8), 2.67 (t, 2H, $^3$J$_{5,6}$ 5.82 Hz, H-5), 1.83-1.76 (m, 4H, H-6, 7), 1.39 (t, 3H, $^3$J$_{16,15}$ 7.14, H-16); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 167.06 (C-2), 163.39 (C-11), 148.08 (C-13), 132.53 (C-17), 132.45 (C-20), 131.08 (C-4), 128.94 (C-19, 21), 127.47 (C-18, 22), 127.06 (C-9), 111.97 (C-3), 60.65 (C-15), 26.45 (C-8), 24.46 (C-5), 23.03 (C-7), 22.89 (C-6), 14.39 (C-16); mass spectrum (ESI), $m/z = 352.09$ (M+23)$^+$ C$_{18}$H$_{19}$NO$_3$S requires 352.10 (M+23)$^+$.

**Ethyl 2-acetamido-5-phenylthiophene-3-carboxylate (54)$^9$**
Yield: 58% (136.7 mg); silica gel TLC $R_f = 0.6$ (30% ethyl acetate in hexanes); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 11.01 (s, 1H, H-6), 7.60 (dd, 2H, $^3$J$_{18/14,17/15}$ 8.44 Hz, $^3$J$_{18/14,16}$ 1.28 Hz, H-18, 14), 7.41 (s, 1H, H-4), 7.39-7.37 (m, 2H, H-15, 17), 7.30-7.27 (s, 2H, H-16), 4.38 (q, 2H, $^3$J$_{11,12}$ 7.15 Hz, H-11), 2.31 (s, 3H, H-19), 1.42 (t, 3H, $^3$J$_{12,11}$ 7.15 Hz); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 148.20 (C-9), 133.86 (C-13), 133.75 (C-5), 129.07 (C-14, 18), 127.55 (C-16), 125.60 (C-17, 15), 119.14 (C-4), 113.48 (C-3), 60.98 (C-11), 23.71 (C-19), 14.51 (C-12); mass spectrum (ESI), $m/z = 312.06$ (M+H)$^+$ C$_{15}$H$_{15}$NO$_3$S requires 312.06 (M+23)$^+$. 

Ethyl 2-benzamido-5-phenylthiophene-3-carboxylate (55)$^9$

Yield: 98% (280 mg); silica gel TLC $R_f = 0.66$ (30% ethyl acetate in hexanes); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 12.06 (s, 1H, H-6), 8.06 (dd, 2H, $^3$J$_{24/20,23/21}$ 8.44 Hz, $^3$J$_{24/20,22}$ 1.47 Hz, H-24, 20), 7.65 (dd, 2H, $^3$J$_{18/14,15/17}$ 8.44 Hz, $^3$J$_{18/14,16}$ 1.28 Hz, H-18, 14), 7.62 (d, $^3$J$_{22,23/21}$ 7.34 Hz, H-22), 7.56 (m, 2H, H-21, 23), 7.41 (m, 2H, H-15, 17), 7.30 (m, 1H, H-16), 4.44 (q, 2H, $^3$J$_{11,12}$ 7.15 Hz, H-11), 1.47 (t, 3H, $^3$J$_{12,11}$ 7.15 Hz, H-12); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 166.16 (C-2), 163.74 (C-7), 148.68 (C-9), 134.13 (C-19), 133.91 (C-13), 132.93 (C-22), 132.16 (C-5), 129.19 (C-17, 15), 129.13 (C-23, 21), 127.68 (C-24, 20), 127.64 (C-16), 125.65 (C-14, 18), 119.44 (C-4), 114.23 (C-
3), 61.15 (C-11), 14.58 (C-12); mass spectrum (ESI), \( m/z = 374.08 \) (M+23)\(^+\) \( \text{C}_{20}\text{H}_{17}\text{NO}_3\text{S} \) requires 374.0827 (M+23)\(^+\).

2-Amino-6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid (41)\(^{10}\)

\[
\begin{aligned}
& \text{Boc} \\
& \text{O} \\
& \text{OH} \\
& \text{NH}_2 \\
& \text{N} \\
& \text{S} \\
\end{aligned}
\]

Yield: 59% (140.0 mg); silica gel TLC \( R_f = 0.54 \) (7% methanol in CH\(_2\)Cl\(_2\)); \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \( \delta \) 11.95 (s, 1H, H-12), 7.29 (s, 2H, H-13), 4.24 (s, 2H, H-8), 3.49 (t, 2H, \( J_{6,5} \) 6Hz, H-6), 2.64 (t, 2H, \( J_{5,6} \) 6Hz, H-5), 1.14 (s, 9H, H-10); \(^{13}\)C-NMR (150 MHz, CDCl\(_3\)): \( \delta \) 166.54 (C-2), 163.44 (C-11), 153.88 (C-13), 130.80 (C-4, 9), 102.61 (C-3), 79.08 (C-15), 42.48 (C-8), 41.45 (C-6), 28.07 (C-20, 19, 16), 14.11 (C-5); mass spectrum (ESI), \( m/z = 321.08 \) (M+23)\(^+\) \( \text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_4\text{S} \) requires 321.08 (M+23)\(^+\).

2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (43)\(^{11}\)

\[
\begin{aligned}
& \text{O} \\
& \text{OH} \\
& \text{NH}_2 \\
\end{aligned}
\]

Yield: 44.4% (1.163g); silica gel TLC \( R_f = 0.11 \) (30% ethyl acetate in hexanes); \(^1\)H-NMR (600 MHz, DMSO-d\(_6\)): \( \delta \) 11.73 (s, 1H, H-12), 7.17 (s, 2H, H-10), 2.57 (m, 2H, H-8), 2.40 (m, 2H, H-5), 2.67 (m, 2H, H-7), 1.63 (m, 2H, H-6); \(^{13}\)C-NMR (150 MHz, DMSO-d\(_6\)): \( \delta \) 167.27 (C-2), 163.24 (C-11), 132.25 (C-9), 115.50 (C-4), 103.59 (C-3), 26.97 (C-8), 24.38 (C-5), 23.35 (C-7), 22.86 (C-6); mass spectrum (ESI), \( m/z = 220.24 \) (M+23)\(^+\) \( \text{C}_8\text{H}_{11}\text{N}_2\text{OS} \) requires 220.04 (M+23)\(^+\).

2-Amino-5-phenylthiophene-3-carboxylic acid (58)\(^{12}\)
Yield: 83% (4.3 g); silica gel TLC $R_f = 0.21$ (30% ethyl acetate in hexanes); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 12.05 (s, 1H, H-8), 7.43 (m, 4H, H-6, 10, 14), 7.32 (m, 2H, H-11, 13), 7.17 (m, 1H, H-12); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 166.10 (C-7), 163.24 (C-2), 133.88 (C-9), 128.97 (C-11, 13), 128.09 (C-12), 123.90 (C-10, 14), 121.79 (C-3), 121.72 (C-5), 105 (C-4); mass spectrum (ESI), $m/z = 242.03$ (M+23)$^+$ C$_{11}$H$_9$NO$_2$S requires 242.02 (M+23)$^+$.

2-Amino-N-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (50)$^{13}"

Yield: 22.08% (70.0 mg); silica gel TLC $R_f = 0.33$ (30% ethyl acetate in hexanes); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 7.35-7.33 (m, 5H, H-16, 17, 18, 19, 20), 6.00 (s, 2H, H-10), 4.59 (d, 2H, 3$^\times$J$_{14,15}$ 5.58 Hz, H-14), 2.60-2.59 (m, 2H, H-8), 2.55-2.54 (m, 2H, H-5), 1.78 (m, 4H, H-6,7) ; $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 166.43 (C-2), 158.66 (C-11), 138.75 (C-9), 128.80 (C-15), 128.74 (C-17, 19), 127.54 (C-16, 20), 127.36 (C-18), 119.31 (C-4), 108.88 (C-3), 43.25 (C-14), 27.24 (C-8), 24.56 (C-5), 22.93 (C-7), 22.85 (C-6); mass spectrum (ESI), $m/z = 309.10$ (M+23)$^+$ C$_{16}$H$_{18}$N$_2$OS requires 309.10 (M+23)$^+$.

2-Amino-N-butyl-5-phenylthiophene-3-carboxamide (59)$^{14}"

5-15
Yield: 61% (152.2 mg); silica gel TLC $R_f = 0.36$ (30% ethyl acetate in hexanes); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 7.43 (d, 2H, $^3$J$_{10/14,11/13}$ 7.34 Hz, H-10, 14), 7.32 (m, 2H, H-11, 13), 7.21 (m, 1H, H-12), 7.00 (s, 1H, H-4) 5.87 (s, 1H, H-15), 3.40 (t, $^3$J$_{16,17}$ 6.97 Hz, H-16), 1.59 (quin, 2H, $^3$J$_{17,18/16}$ 7.34 Hz, H-17), 1.42 (sex, 2H, $^3$J$_{18,17/19}$ 7.70 Hz, H-18), 0.96 (t, $^3$J$_{19,18}$ 7.34 Hz, H-19); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 165.81 (C-7), 158.64 (C-2), 133.94 (C-5), 128.99 (C-11, 13), 126.90 (C-12), 126.50 (C-9), 124.84 (C-14, 10), 118.13 (C-4), 111.02 (C-3), 39.22 (C-16), 32.09 (C-17), 20.34 (C-18), 13.96 (C-19); mass spectrum (ESI), $m/z = 297.10$ (M+23)$^+$. $\text{C}_{15}\text{H}_{18}\text{N}_{2}\text{O}_{5}$ requires 297.1038 (M+23)$^+$. 

\[
\text{structure image}
\]
\(^1\)H-NMR of compound 6-benzyl 3-ethyl 2-amino-4,7-dihydrothieno[2,3-\(c\)]pyridine-3,6(5\(H\))-dicarboxylate (22, CDCl\(_3\))\(^1\)

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S-17
\[^{13}\text{C}-\text{NMR of compound 6-benzyl 3-ethyl 2-amino-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (22, CDCl}_3]\]
$^1$H-NMR of compound 6-(tert-butyl) 3-ethyl 2-amino-4,7-dihydrothieno[2,3-\text{c}]pyridine-3,6(5\text{H})-dicarboxylate (23, CDCl$_3$)²

![Chemical Structure]

Chemical Shift (ppm)
$^{13}\text{C}$-NMR of compound 6-(tert-butyl) 3-ethyl 2-amino-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (23, CDCl$_3$)$^2$
$^1$H-NMR of compound ethyl 2-amino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (24, (CD$_3$)$_2$SO)$^3$
$^{13}$C-NMR of compound ethyl 2-amino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (24, (CD$_3$)$_2$SO)$^3$
COSY of compound ethyl 2-amino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (24, (CD$_3$)$_2$SO)$_3$
$^1$H-NMR of compound ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (25, CDCl$_3$)
$^{13}$C-NMR of compound ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (25, CDCl$_3$)
$^1$H-NMR of compound ethyl 2-amino-5-phenylthiophene-3-carboxylate (26, CDCl$_3$)
$^{13}$C-NMR of compound ethyl 2-amino-5-phenylthiophene-3-carboxylate (26, CDCl$_3$)
$^1$H-NMR of compound 6-(tert-butyl) 3-ethyl 2-acetamido-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (27, CDCl$_3$)$^1$
$^{13}$C-NMR of compound 6-(tert-butyl) 3-ethyl 2-acetamido-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (27, CDCl$_3$)$^1$
COSY of compound 6-(tert-butyl) 3-ethyl 2-acetamido-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (27, CDCl3)
HMQC of compound 6-(<em>tert</em>-butyl) 3-ethyl 2-acetamido-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (27, CDCl₃)¹
$^1$H-NMR of compound 6-(tert-butyl) 3-ethyl 2-benzamido-4,7-dihydrothieno[2,3-$c$]pyridine-3,6($5H$)-dicarboxylate (28, CDCl$_3$)
$^{13}$C-NMR of compound 6-(tert-butyl) 3-ethyl 2-benzamido-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (28, CDCl$_3$)
COSY of compound 6-(tert-butyl) 3-ethyl 2-benzamido-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (28, CDCl₃)
HMOC of compound 6-(tert-butyl) 3-ethyl 2-benzamido-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (28, CDCl₃)
$^1$H-NMR of compound 6-(tert-butyl) 3-ethyl 2-(perfluorobenzamido)-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (29, CDCl$_3$)
$^{13}$C-NMR of compound 6-(tert-butyl) 3-ethyl 2-(perfluorobenzamido)-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (29, CDCl₃)
$^1$H-NMR of compound 6-((tert-butyl) 3-ethyl 2-(3,5-bis(trifluoromethyl)benzamido)-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (30, CDCl$_3$)
$^{13}$C-NMR of compound 6-(tert-butyl) 3-ethyl 2-(3,5-bis(trifluoromethyl)benzamido)-4,7-dihydrothieno[2,3-c]pyridine-3,6(5$H$)-dicarboxylate (30, CDCl$_3$)
COSY of compound 6-(tert-butyl) 3-ethyl 2-(3,5-bis(trifluoromethyl)benzamido)-4,7-dihydrothieno[2,3-c]pyridine-3,6(5H)-dicarboxylate (30)
$^1$H-NMR of compound ethyl 2-acetamido-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (31, CDCl$_3$)$^6$
$^{13}$C-NMR of compound ethyl 2-acetamido-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (31, CDCl$_3$)$^6$
$^1$H-NMR of compound ethyl 2-benzamido-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (32, CDCl$_3$)
$^{13}$C-NMR of compound ethyl 2-benzamido-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (32, CDCl$_3$)
COSY of compound ethyl 2-benzamido-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (32, CDCl3)
\(^1\)H-NMR of compound ethyl 6-ethyl-2-(perfluorobenzamido)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (33, CDCl\(_3\))
\[ ^{13}\text{C-NMR of compound ethyl 6-ethyl-2-(perfluorobenzamido)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (33, CDCl}_3 \]
$^1$H-NMR of compound ethyl 2-(3,5-bis(trifluoromethyl)benzamido)-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (34, CDCl₃)
$^{13}$C-NMR of compound ethyl 2-(3,5-bis(trifluoromethyl)benzamido)-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (34, CDCl$_3$)
COSY of compound ethyl 2-(3,5-bis(trifluoromethyl)benzamido)-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (34, CDCl3)
$^1$H-NMR of compound 2-(3,5-Bis(trifluoromethyl)benzamido)-6-ethyl-N-(4-methylbenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide (35, CDCl$_3$)

Chemical Shift (ppm)

- 8.47 (22.4)
- 8.08 (20)
- 7.77
- 7.25 (32.8)
- 7.19 (32.9)
- 6.23 (23)
- 4.65 (30)
- 3.71 (31)
- 2.87 (5,6)
- 2.89
- 2.71
- 2.72
- 2.36 (34)
- 2.68
- 2.70 (15)
- 1.22
- 1.23 (16)
- 1.24
- 0.89
- 2.01
- 2.11
- 1.96
- 0.98
- 2.05
- 1.95
- 3.87
- 1.98
- 3.11
- 3.05

Chemical Shift (ppm)
$^{13}$C-NMR of compound 2-(3,5-Bis(trifluoromethyl)benzamido)-6-ethyl-N-(4-methylbenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide (35, CDCl$_3$)
COSY of compound 2-(3,5-Bis(trifluoromethyl)benzamido)-6-ethyl-N-(4-methylbenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide (35, CDCl₃)
HMQC of compound 2-(3,5-Bis(trifluoromethyl)benzamido)-6-ethyl-N-(4-methylbenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide (35, CDCl$_3$)
$^1$H-NMR of compound Ethyl 2-acetamido-4,5,6,7-tetrahydrobenzo[$b$] thiophene-3-carboxylate (36, CDCl$_3$)$^7$
\(^{13}\text{C}\)-NMR of compound ethyl 2-acetamido-4,5,6,7-tetrahydrobenzo[\textit{b}] thiophene-3-carboxylate (36, CDCl\textsubscript{3})\textsuperscript{7}
$^1$H-NMR of compound ethyl-2-benzamido-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (37, CDCl$_3$)$^8$
$^{13}$C-NMR of compound ethyl-2-benzamido-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (37, CDCl₃)$^8$
$^1$H-NMR of compound ethyl 2-(perfluorobenzamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (38, CDCl$_3$)
$^{13}$C-NMR of compound ethyl 2-(perfluorobenzamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (38, CDCl$_3$)
$^1$H-NMR of compound ethyl 2-(3,5-bis(trifluoromethyl)benzaimdo)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (39, CDCl₃)
$^{13}$C-NMR of compound ethyl 2-(3,5-bis(trifluoromethyl)benzaimdo)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (39, CDCl$_3$)
$^1$H-NMR of compound ethyl 2-acetamido-5-phenylthiophene-3-carboxylate (54, CDCl$_3$)
$^{13}$C-NMR of compound ethyl 2-acetamido-5-phenylthiophene-3-carboxylate (54, CDCl$_3$)$^9$

![Chemical Shift (ppm)]

Chemical Shift (ppm):
- 14.51 (12)
- 23.71 (19)
- 60.98 (11)
- 77.16 (76.86)
- 113.48 (3)
- 119.14 (4)
- 125.60 (17,15)
- 127.55 (16)
- 129.07 (14,18)
- 133.75 (5)
- 133.86 (13)
- 165.76 (7)
- 167.19 (2)
- 148.20 (9)

![Molecular Structure]

Structure:
- O
- N
- S
- C
- H

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$^1$H-NMR of compound ethyl 2-benzamido-5-phenylthiophene-3-carboxylate (55, CDCl$_3$)$^9$
$^{13}$C-NMR of compound ethyl 2-benzamido-5-phenylthiophene-3-carboxylate (55, CDCl$_3$)$^9$
COSY of compound ethyl 2-benzamido-5-phenylthiophene-3-carboxylate (55, CDCl₃)⁹
HMOC of compound ethyl 2-benzamido-5-phenylthiophene-3-carboxylate (55, CDCl₃)⁹
$^1$H-NMR of compound ethyl 2-(perfluorobenzamido)-5-phenylthiophene-3-carboxylate (56, CDCl$_3$)
$^{13}$C-NMR of compound ethyl 2-(perfluorobenzamido)-5-phenylthiophene-3-carboxylate (56, CDCl$_3$)
$^1$H-NMR of compound ethyl 2-(3,5-bis(trifluoromethyl)benzamido)-5-phenylthiophene-3-carboxylate (57, CDCl$_3$)
$^{13}$C-NMR of compound ethyl 2-(3,5-bis(trifluoromethyl)benzamido)-5-phenylthiophene-3-carboxylate (57, CDCl$_3$)
\(^1\)H-NMR of compound 2-Amino-6-((benzyloxy)carbonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid (40, (CD$_3$)$_2$SO)
$^{13}$C-NMR of compound 2-Amino-6-((benzyloxy)carbonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid (40, (CD$_3$)$_2$SO)
$^1\text{H-NMR}$ of compound 2-Amino-6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid (41, (CD$_3$)$_2$SO)$^{10}$
$^{13}$C-NMR of compound 2-amino-6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid (41, (CD$_3$)$_2$SO)$^{10}$
$^{1}$H-NMR of compound 2-amino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid (42, (CD$_3$)$_2$SO)
$^{13}$C-NMR of compound 2-amino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid (42, (CD$_3$)$_2$SO)
$^1$H-NMR of compound 2-amino-4,5,6,7-tetrahydrobenzo[$b$]thiophene-3-carboxylic acid (43, (CD$_3$)$_2$SO)$^{11}$

Chemical Shift (ppm)

- 4.08
- 2.00
- 1.98
- 1.88
- 0.86

Water
DMSO
\(^{13}\)C-NMR of compound 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid (43, (CD\(_3\))\(_2\)SO)\(^{11}\)
$^1$H-NMR of compound 2-Amino-5-phenylthiophene-3-carboxylic acid (58, (CD$_3$)$_2$SO)$^{12}$
$^{13}$C-NMR of compound 2-Amino-5-phenylthiophene-3-carboxylic acid (58, (CD$_3$)$_2$SO)$^{12}$
$^1$H-NMR of compound 2-amino-$N$-butyl-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide (44, CDCl$_3$)
$^{13}$C-NMR of compound 2-amino-$N$-butyl-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-$c$]pyridine-3-carboxamide (44, CDCl$_3$)
$^1$H-NMR of compound 2-amino-$N$-benzyl-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-$c$]pyridine-3-carboxamide (45, CDCl$_3$)
$^{13}$C-NMR of compound 2-amino-N-benzyl-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide (45, CDCl$_3$)
$^1$H-NMR of compound 2-amino-6-ethyl-N-(4-methylbenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide (46, CDCl$_3$)
\(^{13}\)C-NMR of compound 2-amino-6-ethyl-\(N\)-(4-methylbenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide (46, CDCl\(_3\))
COSY of compound 2-amino-6-ethyl-N-(4-methylbenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide (46, CDCl₃)
$^{1}H$-NMR of compound 2-amino-6-ethyl-$N$-(2-methoxybenzyl)-4,5,6,7-tetrahydrothieno[2,3-\textit{c}]pyridine-3-carboxamide (47, CDCl$_3$)
$^{13}$C-NMR of compound 2-amino-6-ethyl-$N$-(2-methoxybenzyl)-4,5,6,7-tetrahydrothieno[2,3-$c$]pyridine-3-carboxamide (47, CDCl$_3$)
$^1$H-NMR of compound $N$-(adamantan-1-yl)-2-amino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide (48, CDCl$_3$)
$^{13}$C-NMR of compound $N$-(adamantan-1-yl)-2-amino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxamide (48, CDCl$_3$)
$^1$H-NMR of compound 2-amino-N-butyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (49, CDCl$_3$)

![NMR Spectrum]

Chemical Shift (ppm):
- 7.27
- 5.67

3.00 2.08 1.97 3.96 1.94 1.99 1.92 0.97

0.93 0.94 0.96 1.38 1.39 1.40 1.54 1.55 1.56

1.79 1.80 1.80 1.81 2.53 2.54 2.61 3.35 3.36

3.36 3.37 3.38 5.67 7.27

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$^{13}$C-NMR of compound 2-amino-$N$-butyl-4,5,6,7-tetrahydrobenzo[$b$]thiophene-3-carboxamide (49, CDCl$_3$)
$^1$H-NMR of compound 2-amino-$N$-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (50, CDCl$_3$)$^{13}$
$^{13}$C-NMR of compound 2-amino-$N$-benzyl-4,5,6,7-tetrahydrobenzo[$b$]thiophene-3-carboxamide (50, CDCl$_3$)$^{13}$
$^1$H-NMR of compound 2-amino-$N$-(4-methylbenzyl)-4,5,6,7-tetrahydrobenzo[$b$]thiophene-3-carboxamide (51, CDCl$_3$)
$^{13}$C-NMR of compound 2-amino-$N$-(4-methylbenzyl)-4,5,6,7-tetrahydrobenzo[$b$]thiophene-3-carboxamide (51, CDCl$_3$)
\(^1\)H-NMR of compound 2-amino-\(N\)-(2-methoxybenzyl)-4,5,6,7-tetrahydrobenzo[\textit{b}]thiophene-3-carboxamide (52, CDCl\textsubscript{3})
$^{13}$C-NMR of compound 2-amino-$N$-(2-methoxybenzyl)-4,5,6,7-tetrahydrobenzo[$b$]thiophene-3-carboxamide (52, CDCl$_3$)
$^1$H-NMR of compound $N$-(adamantan-1-yl)-2-amino-4,5,6,7-tetrahydrobenzo[$b$]thiophene-3-carboxamide (53, CDCl$_3$)
$^{13}$C-NMR of compound $N$-(adamantan-1-yl)-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (53, CDCl$_3$)
$^1$H-NMR of compound 2-Amino-$N$-butyl-5-phenylthiophene-3-carboxamide (59, CDCl$_3$)$^{14}$
$^{13}$C-NMR of compound 2-Amino-$N$-butyl-5-phenylthiophene-3-carboxamide (59, CDCl$_3$)$^{14}$
\(^1\)H-NMR of compound 2-amino-N-benzyl-5-phenylthiophene-3-carboxamide (60, CDCl₃)
$^{13}$C-NMR of compound 2-amino-$N$-benzyl-5-phenylthiophene-3-carboxamide (60, CDCl$_3$)
$^{1}$H-NMR of compound 2-amino-$N$-(4-methylbenzyl)-5-phenylthiophene-3-carboxamide (61, CDCl$_3$)
\(^{13}\text{C-NMR of compound 2-amino-\textit{N}-(4-methylbenzyl)-5-phenylthiophene-3-carboxamide (61, CDCl}_3\)\)
$^1$H-NMR of compound 2-Amino-N-(2-methoxybenzyl)-5-phenylthiophene-3-carboxamide (62, CDCl$_3$)
$^{13}$C-NMR of compound 2-Amino-$N$-(2-methoxybenzyl)-5-phenylthiophene-3-carboxamide (62, CDCl$_3$)
$^1$H-NMR of compound $N$-(adamantan-1-yl)-2-amino-5-phenylthiophene-3-carboxamide (63, CDCl$_3$)
$^{13}$C-NMR of compound $N$-(adamantan-1-yl)-2-amino-5-phenylthiophene-3-carboxamide (63, CDCl$_3$)
References


