

SUPPORTING INFORMATION:

N-methyl dihydroquinazolinones derivatives of Retro-2 with enhanced efficacy against Shiga toxin

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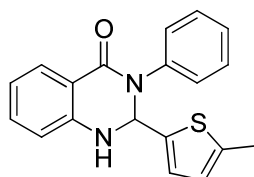
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Contents:

Chemical Synthesis

Chemical synthesis

2-(5-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (1)



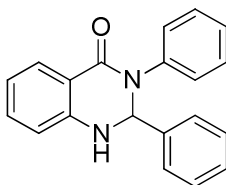
To a solution of 2-aminobenzanilide (1.0 g, 4.71 mmol) in methanol (2 3mL, 0.2 M) was added 5-methylthiophen-2-carboxaldehyde (515 μ L, 4.71 mmol) and the solution was stirred at room temperature until complete consumption of starting materials. The precipitate was filtered to give the title compound (708 mg, 47 %) as a white solid.

¹H-NMR (400MHz, MeOD) δ (ppm) = 0.76 (s, 3H), 4.68 (s, 1H), 4.90-4.91 (m, 1H), 5.08 (d, J = 3.2 Hz, 1H), 5.19 (d, J = 8.0 Hz, 1H), 5.25 (t, J = 7.2 Hz, 1H), 5.68-5.81 (m, 6H), 6.23 (dd, J = 1.2 Hz and J = 7.6 Hz, 1H).

MS (ESI) $[M+H]^+$ = 320.9

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 7.40 min, m/z : 320.9 ($[M+H]^+$)

2,3-diphenyl-2,3-dihydroquinazolin-4(1H)-one (8)



The title compound was prepared following the same general protocol as described for compound **1** using 2-aminobenzanilide (212 mg, 1.0 mmol), benzaldehyde (105 μ L, 1.033 mmol). The filtration yielded the title compound (253 mg, 84 %) as a white solid.

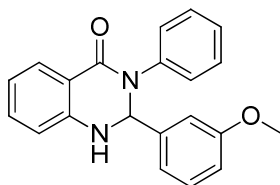
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 6.27 (d, J = 2.6 Hz, 1H), 6.71 (td, J = 8.0 Hz, J' = 0.9 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 7.15-7.21 (m, 1H), 7.22-7.40 (m, 10H), 7.62 6.27 (d, J = 2.6 Hz, 1H), 7.72 (dd, J = 8.0 Hz, J' = 0.9 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 72.5, 114.7, 115.2, 117.4, 125.9, 126.1, 126.5, 127.9, 128.2, 128.3, 128.5, 133.7, 140.6, 140.7, 146.5, 162.2.

MS (ESI) [M+H]⁺ = 301.1

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 7.00 min, m/z : 301.1 ([M+H⁺])

2-(3-methoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (9)



The title compound was prepared following the same general protocol as described for compound **1** using 2-aminobenzanilide (212 mg, 1.0 mmol), *o*-anisaldehyde (136 mg, 1.0 mmol). The filtration yielded the title compound (292 mg, 88 %) as a white solid.

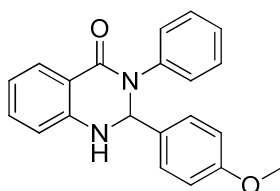
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 3.76 (s, 3H), 6.42 (d, J = 2.7 Hz, 1H), 6.71 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.86 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 7.16-7.34 (m, 9H), 7.75 (dd, J = 8.0 Hz, J' = 1.6 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) =55.5, 68.1, 111.3, 114.8, 117.3, 120.0, 126.1, 126.3, 126.5, 127.5, 127.8, 128.5, 129.7, 133.6, 140.7, 146.5, 155.9, 162.3

MS (ESI) [M+H]⁺ = 331.2

LC/MS (XBridge 100 × 4.6 mm) : t_R = 7.28 min, m/z : 331.2 ([M+H]⁺)

2-(4-methoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (10)



The title compound was prepared following the same general protocol as described for compound **1** using 2-aminobenzanilide (212 mg, 1.0 mmol), *p*-anisaldehyde (125 μL, 1.027 mmol). The filtration yielded the title compound (257 mg, 78%) as a white solid.

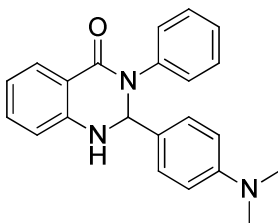
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 3.68 (s, 3H), 6.22 (d, *J* = 2.6 Hz, 1H), 6.71 (td, *J* = 7.5 Hz, *J*' = 0.9 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.82-6.87 (m, 2H), 7.15-7.36 (m, 8H), 7.56 (d, *J* = 2.6 Hz, 1H), 7.72 (dd, *J* = 7.8 Hz, *J*' = 1.6 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 55.0, 72.2, 113.6, 114.7, 115.2, 117.3, 125.9, 126.2, 127.8, 128.5, 132.5, 133.6, 140.7, 146.6, 159.0, 162.2

MS (ESI) [M+H]⁺ = 331.1

LC/MS (XBridge 100 × 4.6 mm) : t_R = 6.95 min, m/z : 331.2 ([M+H]⁺)

2-(4-(dimethylamino)phenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (11)



The title compound was prepared following the same general protocol as described for compound **1** using 2-aminobenzanilide (212 mg, 1.0 mmol), 4-(dimethylamino)benzaldehyde (149 mg, 1.0 mmol). The filtration yielded the title compound (263 mg, 77%) as a pale beige solid.

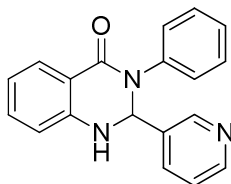
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 2.82 (s, 6H), 6.13 (d, *J* = 2.6 Hz, 1H), 6.58-6.63 (m, 2H), 6.67-6.72 (m, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 7.14-7.20 (m, 3H), 7.22-7.28 (m, 3H), 7.29-7.34 (m, 2H), 7.49 (d, *J* = 2.6 Hz, 1H), 7.72 (dd, *J* = 7.8 Hz, *J'* = 1.6 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 73.0, 112.2, 115.2, 115.8, 117.6, 126.2, 126.6, 127.7, 128.2, 128.3, 128.9, 134.0, 141.4, 147.2, 150.6, 162.8

MS (ESI) [M+H]⁺ = 344.2

LC/MS (XBridge 100 × 4.6 mm) : *t_R* = 6.57 min, *m/z* : 344.2 ([M+H]⁺)

3-phenyl-2-(pyridin-3-yl)-2,3-dihydroquinazolin-4(1H)-one (12)



The title compound was prepared following the same general protocol as described for compound **1** using 2-aminobenzanilide (212 mg, 1.0 mmol), 3-pyridinecarboxaldehyde (95 μL, 1.007 mmol). The filtration yielded the title compound (144 mg, 78%) as a beige solid.

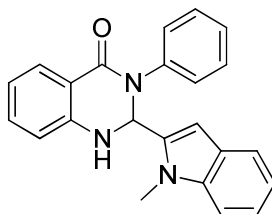
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 6.44 (d, *J* = 2.6 Hz, 1H), 6.76 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 7.17-7.37 (m, 7H), 7.70 (d, *J* = 2.6 Hz, 1H), 7.75 (dd, *J* = 7.8 Hz, *J*' = 1.4 Hz, 1H), 7.78 (dt, *J* = 8.0 Hz, *J*' = 2.0 Hz, 1H), 8.45 (dd, *J* = 4.8 Hz, *J*' = 1.6 Hz, 1H), 8.56 (d, *J* = 2.6 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 70.7, 114.9, 115.3, 117.9, 123.4, 126.2, 126.4, 128.0, 128.7, 133.9, 134.2, 135.8, 140.3, 146.4, 148.1, 149.5, 162.1.

MS (ESI) [M+H]⁺ = 302.2

LC/MS (XBridge 100 × 4.6 mm) : t_R = 4.87 min, m/z : 302.2 ([M+H⁺])

2-(1-methyl-1H-indol-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (13)



To a solution of 2-aminobenzanilide (212 mg, 1.0 mmol) in methanol (0.2 M) was added 1-methylindole-3-carboxaldehyde (159 mg, 1.0 mmol) and the solution was stirred at room temperature until complete consumption of starting materials. The precipitate was filtered to give the title compound (296 mg, 84%) as a white solid.

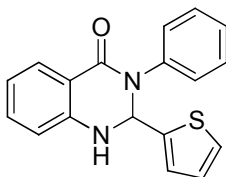
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 3.66 (s, 3H), 6.55 (d, *J* = 2.7 Hz, 1H), 6.69-6.76 (m, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 7.10-7.16 (m, 2H), 7.20-7.35 (m, 7H), 7.46 (d, *J* = 2.7 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.77 (dd, *J* = 8.0 Hz, *J*' = 1.6 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 32.3, 67.6, 109.8, 113.3, 114.7, 115.5, 117.1, 118.9, 119.6, 121.4, 125.2, 125.7, 126.1, 127.9, 128.3, 128.7, 133.3, 136.8, 140.8, 146.7, 162.3.

MS (ESI) [M+H]⁺ = 354.8

LC/MS (XBridge 100 × 4.6 mm) : $t_R = 7.35$ min, $m/z : 354.7$ ($[M+H]^+$)

3-phenyl-2-(thiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (14)



The title compound was prepared following the same general protocol as described for compound 1 using 2-aminobenzanilide (212 mg, 1.0 mmol), thiophen-2-carboxaldehyde (85 μ L, 1.016 mmol). The filtration yielded the title compound (238 mg, 78%) as a beige solid.

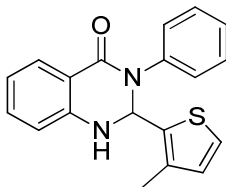
$^1\text{H-NMR}$ (400MHz, DMSO-d_6) δ (ppm) = 6.54 (d, $J = 2.8$ Hz, 1H), 6.78 (t, $J = 7.8$ Hz, 1H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.88 (dd, $J = 5.0$ Hz, $J' = 3.6$ Hz, 1H), 6.96 (d, $J = 3.6$ Hz, 1H), 7.21-7.40 (m, 7H), 7.70 (d, $J = 2.8$ Hz, 1H), 7.75 (dd, $J = 8.0$ Hz, $J' = 1.4$ Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO-d_6) δ (ppm) = 69.4, 115.2, 115.5, 118.0, 125.8, 126.2, 126.3, 126.4, 127.9, 128.6, 133.7, 146.3, 161.5.

MS (ESI) $[M+H]^+ = 307.2$

LC/MS (XBridge 100 × 4.6 mm) : $t_R = 6.85$ min, $m/z : 307.2$ ($[M+H]^+$)

2-(3-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (15)



The title compound was prepared following the same general protocol as described for compound **1** using 2-aminobenzanilide (212 mg, 1.0 mmol), 3-methyl-2-thiophencarboxaldehyde (110 μ L, 1.020 mmol). The filtration yielded the title compound (272 mg, 85%) as a beige solid.

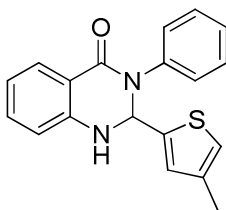
$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ (ppm) = 1.91 (s, 3H), 6.54 (d, J = 2.3 Hz, 1H), 6.67 (d, J = 5.0 Hz, 1H), 6.76-6.83 (m, 2H), 7.18-7.37 (m, 7H), 7.49 (d, J = 2.0Hz, 1H), 7.74 (dd, J = 7.8 Hz, J' =1.5 Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ (ppm) =13.2, 67.8, 114.8, 115.0, 117.7, 124.1, 126.6, 127.4, 127.8, 128.5, 129.4, 133.7, 135.0, 136.9, 140.1, 146.5, 161.7.

MS (ESI) $[\text{M}+\text{H}]^+ = 312.1$

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 7.08$ min, m/z : 312.1 ($[\text{M}+\text{H}^+]$)

2-(4-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (16)



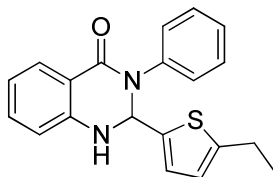
The title compound was prepared following the same general protocol as described for compound **1** using 2-aminobenzanilide (212 mg, 1.0 mmol), 4-methylthiophen-2-carboxaldehyde (110 μ L, 1.020 mmol). The filtration yielded the title compound (209 mg, 65%) as a white solid.

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ (ppm) = 2.07 (s, 3H), 6.45 (d, J = 3.0 Hz, 1H), 6.74-6.80 (m, 2H), 6.82 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 1.2 Hz, 1H), 7.21-7.41 (m, 6H), 7.64 (d, J = 3.0 Hz, 1H), 7.73 (dd, J = 8.0 Hz, J' =1.6 Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ (ppm) = 15.2, 69.3, 115.2, 115.5, 117.9, 120.8, 126.1, 126.2, 127.9, 128.2, 128.6, 133.7, 136.1, 140.4, 144.5, 146.2, 161.4.

MS (ESI) [M+H]⁺ = 321.1

2-(5-ethylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (17)



The title compound was prepared following the same general protocol as described for compound 1 using 2-aminobenzanilide (212 mg, 1.0 mmol), 5-ethylthiophen-2-carboxaldehyde (125 μ L, 1.0 mmol). The filtration yielded the title compound (174 mg, 52%) as a beige solid.

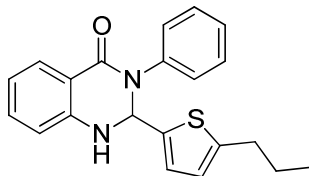
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 1.13 (t, J = 7.6 Hz, 3H); 2.67 (q, J = 7.6 Hz, 2H); 6.42 (d, J = 2.4 Hz, 1H); 6.58 (d, J = 3.2 Hz, 1H); 6.74-6.83 (m, 3H); 7.24 (t, J = 7.2 Hz, 1H); 7.30-7.40 (m, 5H); 6.64 (d, J = 2.8 Hz, 1H); 7.73 (d, J = 7.2 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 15.5, 22.6, 69.6, 115.1, 115.4, 117.9, 122.6, 126.0, 126.2, 126.3, 127.9, 128.6, 133.7, 140.4, 141.6, 146.2, 146.6, 161.4.

MS (ESI) [M+H]⁺ = 335.1

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 7.57 min, m/z : 335.1 ([M+H]⁺)

3-phenyl-2-(5-propylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (18)



To a solution of 2-aminobenzanilide (212 mg, 1.0 mmol) and 5-propylthiophene-2-carbaldehyde (154 mg, 1.0 mmol) in methanol (5 mL, 0.2 M) was stirred at room temperature for 5 days. The mixture was filtered through a short pad of silica gel and the filtrate was then concentrated under reduced pressure to yield the title compound (341 mg, 98%) as a yellow oil.

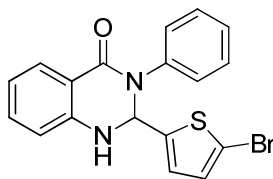
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 0.82 (t, *J* = 7.4 Hz, 3H), 1.49 (sex, *J* = 7.4 Hz, 2H), 2.60 (t, *J* = 7.4 Hz, 2H), 6.40 (d, *J* = 2.7 Hz, 1H), 6.54 (d, *J* = 3.5 Hz, 1H), 6.72 (d, *J* = 3.5 Hz, 1H), 6.75-6.78 (m, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 7.21-7.40 (m, 6H), 7.62 (d, *J* = 2.8 Hz, 1H), 7.73 (dd, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 13.5, 24.3, 31.3, 69.8, 115.22, 115.5, 118.0, 123.4, 126.2, 126.4, 133.8, 138.7, 138.8, 140.5, 141.7, 144.9, 146.4, 161.6

MS (ESI) [M+H]⁺ = 349.5

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.80 min, m/z : 349.5 ([M+H⁺])

2-(5-bromothiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (19)



The title compound was prepared following the same general protocol as described for compound **1** using 2-aminobenzanilide (212 mg, 1.0 mmol), 5-bromo-2-thiophenecarboxaldehyde (119 μL, 1.001 mmol). The filtration yielded the title compound (327 mg, 85%) as a white solid.

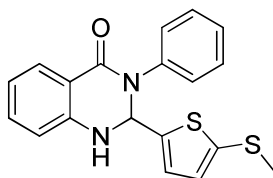
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 6.51 (d, *J* = 2.8 Hz, 1H), 6.67-6.84 (m, 2H), 6.85 (d, *J* = 8.0Hz, 1H), 7.00 (d, *J* = 3.8 Hz, 1H), 7.23-7.43 (m, 6H), 7.71-7.77 (m, 2H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 69.3, 110.7, 115.4, 115.5, 118.4, 126.4, 126.5, 127.3, 128.0, 128.8, 129.6, 134.0, 140.1, 146.0, 146.3, 161.3.

MS (ESI) [M+H]⁺ = 385.0, 387.0

LC/MS (XBridge 100 × 4.6 mm) : t_R = 9.47 min, m/z : 385.5, 387.0 ([M+H]⁺)

2-(5-(methylthio)thiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (20)



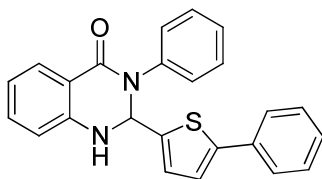
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 2.39 (s, 3H), 6.49 (d, J = 2.9 Hz, 1H), 6.77-6.90 (m, 4H), 7.22-7.28 (m, 1H), 7.32-7.42 (m, 5H), 7.73 (d, J = 3.0 Hz, 1H), 7.77 (dd, J = 7.8 Hz, J' = 1.5 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 20.6, 69.6, 115.4, 115.6, 118.3, 126.4, 126.5, 127.0, 128.8, 133.9, 136.6, 140.4, 145.9, 146.2, 161.5

MS (ESI) [M+H]⁺ = 353.0

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.20 min, m/z : 353.0 ([M+H]⁺)

3-phenyl-2-(5-phenylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (21)

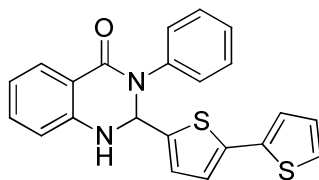


¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 6.54 (d, J = 2.8Hz, 1H); 6.80 (t, J = 7.6Hz, 1H); 6.86 (d, J = 8.0Hz, 1H); 6.96 (d, J = 3.6Hz, 1H); 7.24-7.29 (m, 3H); 7.33-7.42 (m, 7H); 7.52 (d, J = 7.6 Hz, 2H); 7.74 (d, J = 2.8Hz, 1H); 7.77 (d, J = 7.2 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 71.0, 115.7, 117.0, 119.9, 120.7, 122.2, 125.8, 126.3, 126.8, 127.0, 127.5, 127.8, 128.9, 129.1, 129.3, 134.0, 140.6, 143.1, 144.7, 145.2, 162.6

MS (ESI) [M+H]⁺ = 383.1

2-([2,2'-bithiophen]-5-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (22)



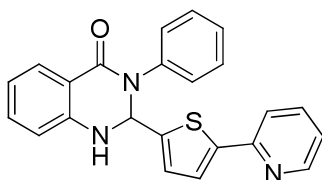
¹H-NMR (400MHz, CDCl₃) δ (ppm) = 5.29 (s, 1H), 6.18 (s, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.75 (d, J = 3.7 Hz, 1H), 6.84 (d, J = 3.7 Hz, 1H), 6.89-6.97 (m, 2H), 7.02-7.05 (m, 1H), 7.17 (dd, J = 5.1 Hz, J' = 1.2 Hz, 1H), 7.20-7.27 (m, 1H), 7.29-7.38 (m, 5H), 8.02 (dd, J = 7.8 Hz, J' = 1.6 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 71.0, 115.7, 117.1, 120.1, 120.7, 122.8, 124.2, 124.9, 126.8, 127.1, 127.3, 127.9, 129.1, 129.2, 134.1, 136.8, 140.5, 142.6, 145.0, 162.5.

MS (ESI) [M+H]⁺ = 389.1

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.60 min, m/z : 389.1 ([M+H]⁺)

3-phenyl-2-(5-(pyridin-2-yl)thiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (23)



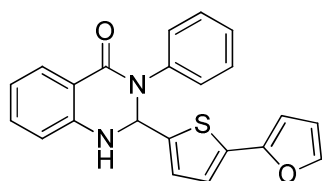
¹H-NMR (400MHz, CDCl₃) δ (ppm) = 5.47 (s, 1H), 6.20 (d, *J* = 3.1 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.84-6.90 (m, 2H), 7.00 (ddd, *J* = 7.4 Hz, *J'* = 4.8 Hz, *J''* = 1.0 Hz, 1H), 7.17-7.23 (m, 1H), 7.23-7.35 (m, 6H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.60 (td, *J* = 7.9 Hz, *J'* = 1.8 Hz, 1H), 8.00 (dd, *J* = 7.8 Hz, *J'* = 1.6 Hz, 1H), 8.46-8.49 (m, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 70.7, 115.7, 117.1, 118.7, 119.9, 122.1, 123.8, 126.5, 126.8, 127.5, 128.9, 129.0, 133.9, 136.7, 140.5, 144.8, 144.9, 145.9, 149.4, 151.9, 162.4

MS (ESI) [M+H]⁺ = 384.5

LC/MS (XBridge 100 × 4.6 mm) : *t_R* = 7.67 min, *m/z* : 384.5 ([M+H]⁺)

2-(5-(furan-2-yl)thiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (24)



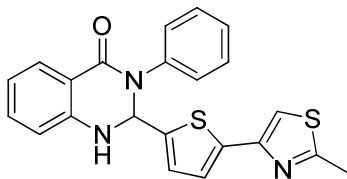
¹H-NMR (400MHz, CDCl₃) δ (ppm) = 5.25 (s, 1H), 6.19 (s, 1H), 6.36-6.42 (m, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 3.7 Hz, 1H), 6.88-6.94 (m, 2H), 7.19-7.37 (m, 7H), 8.01 (d, *J* = 7.9 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 71.0, 77.2, 105.7, 111.8, 115.7, 117.2, 120.1, 121.6, 126.9, 127.2, 127.3, 129.1, 129.2, 134.1, 140.5, 142.0, 142.4, 145.0, 148.9, 162.5

MS (ESI) [M+H]⁺ = 373.1

LC/MS (XBridge 100 × 4.6 mm) : *t_R* = 8.27 min, *m/z* : 373.1 ([M+H]⁺)

2-(5-(2-methylthiazol-4-yl)thiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (25)



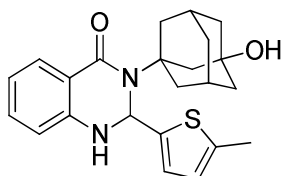
¹H-NMR (400MHz, CDCl₃) δ (ppm) = 2.67 (s, 3H), 6.20 (s, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 3.8 Hz, 1H), 6.85-6.91 (m, 1H), 7.06 (s, 1H), 7.08 (d, *J* = 3.8 Hz, 1H), 7.18-7.24 (m, 1H), 7.26-7.33 (m, 5H), 8.00 (dd, *J* = 7.8 Hz, *J*' = 1.6 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 19.2, 70.9, 111.8, 115.7, 117.1, 120.0, 123.1, 126.8, 127.0, 127.3, 129.0, 129.1, 134.0, 138.6, 140.5, 143.4, 145.0, 148.9, 162.5, 166.4

MS (ESI) [M+H]⁺ = 404.0

LC/MS (XBridge 100 × 4.6 mm) : t_R = 7.98 min, m/z : 404.0 ([M+H]⁺)

3-((1r,3s,5R,7S)-3-hydroxyadamantan-1-yl)-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (26)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-N-(3-hydroxyadamantan-1-yl)benzamide (201 mg, 0.702 mmol), 5-methylthiophen-2-carboxaldehyde (77 μL, 0.705 mmol). The filtration yielded the title compound (223 mg, 81%) as a pale yellow solid.

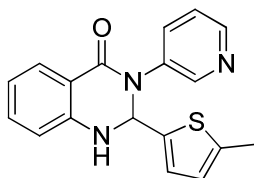
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 4.41-1.63 (m, 6H), 1.90-2.02 (m, 6H), 2.12-2.21 (s, 2H), 2.55 (s, 3H), 4.52 (s, 1H), 6.99-7.02 (m, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.31 (td, *J* = 7.6 Hz, *J'* = 1.1 Hz, 1H), 7.50 (td, *J* = 7.6 Hz, *J'* = 1.6 Hz, 1H), 7.62 (d, *J* = 3.6 Hz, 1H), 7.95 (dd, *J* = 7.6 Hz, *J'* = 1.6 Hz, 1H), 8.66 (s, 1H), 8.68 (s, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 15.7, 30.1, 34.9, 44.2, 49.4, 53.5, 67.3, 119.4, 125.9, 127.3, 128.0, 129.9, 131.8, 136.0, 139.2, 147.3, 148.5, 155.5, 164.0

MS (ESI) [M+H]⁺ = 395.1

LC/MS (XBridge 100 × 4.6 mm) : t_R = 7.48 min, m/z : 395.1 ([M+H]⁺)

2-(5-methylthiophen-2-yl)-3-(pyridin-3-yl)-2,3-dihydroquinazolin-4(1H)-one (37)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-N-(pyridin-3-yl)benzamide (340 mg, 1.594 mmol), 5-methylthiophen-2-carboxaldehyde (174 μL, 1.593 mmol). The filtration yielded the title compound (172 mg, 34%) as a pale yellow solid.

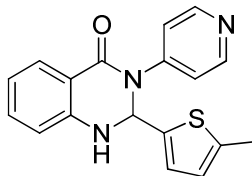
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 2.31 (s, 3H), 6.53-6.58 (m, 2H), 6.75 (d, *J* = 3.5 Hz, 1H), 6.77-6.82 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 7.35 (td, *J* = 7.9 Hz, *J'* = 1.6 Hz, 1H), 7.31 (dd, *J* = 8.0 Hz, *J'* = 4.2 Hz, 1H), 7.70-7.76 (m, 3H), 7.31 (dd, *J* = 4.2 Hz, *J'* = 1.6 Hz, 1H), 8.52 (d, *J* = 2.5 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 14.9, 69.3, 114.7, 115.2, 118.0, 123.6, 124.4, 126.7, 127.9, 134.1, 136.7, 139.6, 141.2, 146.6, 146.9, 147.6, 161.9

MS (ESI) $[M+H]^+ = 322.3$

LC/MS (XBridge 100 × 4.6 mm) : $t_R = 5.80$ min, $m/z : 322.3$ ($[M+H]^+$)

2-(5-methylthiophen-2-yl)-3-(pyridin-4-yl)-2,3-dihydroquinazolin-4(1H)-one (38)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-N-(pyridin-4-yl)benzamide (207 mg, 0.970 mmol), 5-methylthiophen-2-carboxaldehyde (128 μ L, 1.17 mmol). The filtration yielded the title compound (201 mg, 64%) as a pale yellow solid.

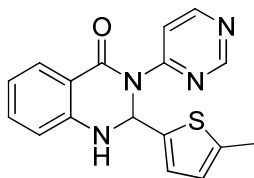
$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ (ppm) = 2.29 (s, 3H), 6.56-6.60 (m, 1H), 6.66 (d, $J = 3.6$ Hz, 1H), 6.76-6.83 (m, 2H), 6.86 (d, $J = 8.0$ Hz, 1H), 7.36 (td, $J = 7.7$ Hz, $J' = 1.6$ Hz, 1H), 7.46-7.51 (m, 2H), 7.77 (dd, $J = 8.0$ Hz, $J' = 1.5$ Hz, 1H), 7.86 (d, $J = 3.6$ Hz, 1H), 8.53-8.59 (m, 2H)

$^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ (ppm) = 14.8, 67.7, 115.1, 115.5, 118.2, 124.7, 126.3, 128.1, 134.4, 139.4, 141.4, 146.1, 147.4, 149.7, 161.8

MS (ESI) $[M+H]^+ = 322.2$

LC/MS (XBridge 100 × 4.6 mm) : $t_R = 5.40$ min, $m/z : 322.2$ ($[M+H]^+$)

2-(5-methylthiophen-2-yl)-3-(pyrimidin-4-yl)-2,3-dihydroquinazolin-4(1H)-one (39)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-N-(pyrimidin-4-yl)benzamide (178 mg, 0.835 mmol), 5-methylthiophen-2-carboxaldehyde (92 μ L, 0.842 mmol). The filtration yielded the title compound (62 mg, 53%) as a pale yellow solid.

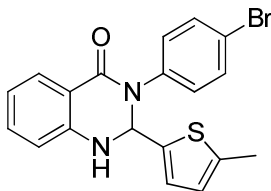
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 2.28 (s, 3H), 6.52-6.56 (m, 1H), 6.66-6.70 (m, 1H), 6.80 (t, J = 7.4 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 7.37-7.47 (m, 2H), 7.77 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 4.2 Hz, 1H), 8.24 (d, J = 5.9 Hz, 1H), 8.72 (d, J = 5.9 Hz, 1H), 9.03 (s, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 14.7, 63.0, 112.8, 114.9, 115.6, 118.2, 124.6, 125.8, 128.5, 135.1, 139.1, 141.3, 146.8, 156.8, 157.7, 157.9, 162.9

MS (ESI) [M+H]⁺ = 323.0

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 6.92 min, m/z : 323.0 ([M+H]⁺)

3-(4-bromophenyl)-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (40)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-N-(4-bromophenyl)benzamide (291 mg, 1.0 mmol), 5-methylthiophen-2-

carboxaldehyde (110 μ L, 1.007 mmol). The filtration yielded the title compound (321 mg, 80%) as a white solid.

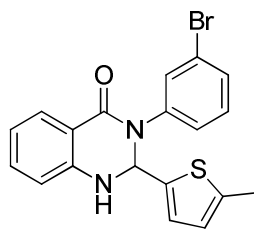
$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ (ppm) = 2.31 (s, 3H), 6.44 (d, J = 2.7 Hz, 1H), 6.55 (dd, J = 3.4 Hz, J' = 1.2 Hz, 1H), 6.72 (d, J = 3.4 Hz, 1H), 6.77 (td, J = 7.7 Hz, J' = 1.0Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 7.24-7.37 (m, 3H), 7.54-7.59 (m, 2H), 7.65 (d, J = 2.7 Hz, 1H), 7.72 (dd, J = 8.0 Hz, J' = 1.6Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ (ppm) = 14.9, 69.4, 115.2, 115.2, 118.0, 118.8, 124.5, 126.5, 127.9, 128.6, 131.6, 134.0, 139.4, 139.6, 141.6, 146.4, 161.5

MS (ESI) $[\text{M}+\text{H}]^+$ = 398.8, 400.8

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 8.42 min, m/z : 398.8, 400.8 ($[\text{M}+\text{H}]^+$)

3-(3-bromophenyl)-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (41)



The title compound was prepared following the same general protocol as described for compound 1 using 2-amino-N-(3-bromophenyl)benzamide (291 mg, 1.0 mmol), 5-methylthiophen-2-carboxaldehyde (110 μ L, 1.007 mmol). The filtration yielded the title compound (363 mg, 91%) as a white solid.

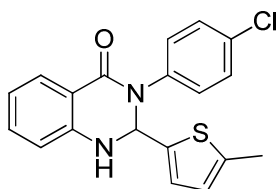
$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ (ppm) = 2.32 (s, 3H), 6.50 (d, J = 2.8 Hz, 1H), 6.57 (dd, J = 3.5 Hz, J' = 1.2Hz, 1H), 6.75 (d, J = 3.5 Hz, 1H), 6.78 (td, J = 7.5 Hz, J' = 1.0Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 7.30-7.37 (m, 3H), 7.43-7.46 (m, 1H), 7.52-7.56 (m, 1H), 7.67 (d, J = 3.0 Hz, 1H), 7.72 (dd, J = 8.0 Hz, J' = 1.6Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 14.9, 69.3, 115.3, 118.0, 121.0, 124.5, 125.3, 126.5, 128.0, 129.1, 130.5, 134.0, 139.4, 141.6, 141.8, 146.4, 161.6

MS (ESI) [M+H]⁺ = 398.8, 400.8

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.58 min, m/z : 398.8, 400.8 ([M+H]⁺)

3-(4-chlorophenyl)-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (43)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-N-(4-chlorophenyl)benzamide (246 mg, 0.997 mmol), 5-methylthiophen-2-carboxaldehyde (110 μL, 1.007 mmol). The filtration yielded the title compound (317 mg, 89%) as a white solid

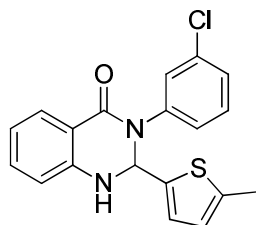
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 2.31 (s, 3H), 6.50 (d, *J* = 2.7 Hz, 1H), 6.55 (dd, *J* = 3.4 Hz, *J*' = 1.2 Hz, 1H), 6.72 (d, *J* = 3.5 Hz, 1H), 6.78 (td, *J* = 7.7 Hz, *J*' = 1.0Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 7.30-7.37 (m, 3H), 7.43-7.46 (m, 2H), 7.66(d, *J* = 3.0 Hz, 1H), 7.72 (dd, *J* = 8.0 Hz, *J*' = 1.6Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 14.9, 69.5, 115.2, 115.2, 118.0, 124.5, 126.5, 127.9, 128.3, 128.6, 130.5, 133.9, 139.2, 139.4, 141.6, 146.4, 161.6

MS (ESI) [M+H]⁺ = 353.1

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.33 min, m/z : 353.1 ([M+H]⁺)

3-(3-chlorophenyl)-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (44)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-N-(3-chlorophenyl)benzamide (291 mg, 1.000 mmol), 5-methylthiophen-2-carboxaldehyde (110 μ L, 1.007 mmol). The filtration yielded the title compound (324 mg, 91%) as a white solid.

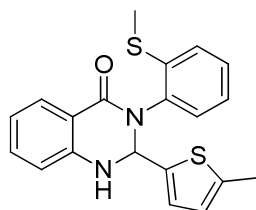
¹H-NMR (400MHz, DMSO-*d*₆) δ (ppm) = 2.32 (s, 3H), 6.51 (d, *J* = 2.8 Hz, 1H), 6.56-6.58 (m, 1H), 6.74-6.80 (m, 2H), 6.83 (d, *J* = 8.1 Hz, 1H), 7.26-7.43 (m, 5H), 7.68 (d, *J* = 2.8 Hz, 1H), 7.72 (dd, *J* = 8.1 Hz, *J'* = 1.3 Hz, 1H)

¹³C-NMR (100MHz, DMSO-*d*₆) δ (ppm) = 14.9, 69.3, 115.2, 115.3, 118.0, 124.5, 124.9, 126.2, 126.3, 126.5, 128.0, 130.2, 134.0, 132.7, 134.0, 139.4, 141.6, 146.4, 161.7

MS (ESI) [M+H]⁺ = 353.1

LC/MS (XBridge 100 \times 4.6 mm) : *t*_R = 8.65 min, *m/z* : 353.1 ([M+H]⁺)

3-(2-(methylthio)phenyl)-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (46)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-N-(2-(methylthio)phenyl)benzamide (215 mg, 0.832 mmol), 5-methylthiophen-2-

carboxaldehyde (91 μ L, 0.833 mmol). The filtration yielded the title compound (241 mg, 79%) as a white solid.

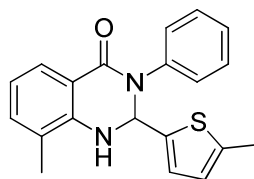
$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ (ppm) = 2.33 (s, 3H), 2.45 (s, 3H), 6.04 (d, J = 2.5 Hz, 1H), 6.51-6.58 (m, 1H), 6.67 (d, J = 3.4 Hz, 1H), 6.73-6.82 (m, 3H), 7.04-7.13 (m, 1H), 7.30-7.37 (m, 3H), 7.60 (d, J = 2.5 Hz, 1H), 7.70 (dd, J = 7.1 Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ (ppm) = 13.7, 14.9, 68.8, 114.6, 114.8, 117.6, 124.2, 124.4, 125.3, 126.5, 127.8, 128.5, 130.2, 133.9, 136.4, 137.2, 139.1, 141.4, 146.5, 161.1

MS (ESI) $[\text{M}+\text{H}]^+ = 366.9$

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 7.88$ min, m/z : 366.9 $[\text{M}+\text{H}]^+$

8-methyl-2-(5-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (47)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-3-methyl-N-phenylbenzamide (206 mg, 0.910 mmol), 5-methylthiophen-2-carboxaldehyde (100 μ L, 0.915 mmol). The filtration yielded the title compound (300 mg, 99%) as a white solid.

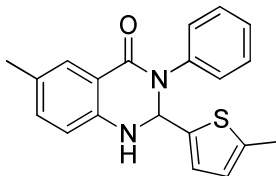
$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ (ppm) = 2.15 (s, 3H), 2.30 (s, 3H), 6.33 (d, J = 4.2 Hz, 1H), 6.53-6.56 (m, 1H), 6.70-6.76 (m, 2H), 7.18 (d, J = 4.2 Hz, 1H), 7.20-7.28 (m, 2H), 7.34-7.45 (m, 4H), 7.62 (d, J = 7.3 Hz, 1H),

$^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ (ppm) = 14.9, 16.8, 69.3, 116.5, 118.2, 123.9, 124.7, 125.6, 125.8, 126.0, 126.1, 128.8, 134.3, 139.2, 140.7, 142.8, 143.8, 161.7

MS (ESI) [M+H]⁺ = 335.1

LC/MS (XBridge 100 × 4.6 mm) : t_R = 7.63 min, m/z : 335.1 ([M+H]⁺)

6-methyl-2-(5-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (48)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-5-methyl-N-phenylbenzamide (212 mg, 0.937 mmol), 5-methylthiophen-2-carboxaldehyde (105 μL, 0.961 mmol). The filtration yielded the title compound (223 mg, 71%) as a white solid

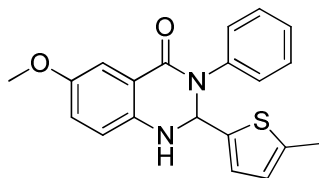
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 2.22 (s, 3H), 2.30 (s, 3H), 6.35 (d, *J* = 2.8 Hz, 1H), 6.52-6.55 (m, 1H), 6.71 (d, *J* = 3.4 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 7.15 (dd, *J* = 8.2 Hz, *J*' = 1.9 Hz, 1H), 7.21-7.26 (m, 1H), 7.27-7.34 (m, 2H), 7.35-7.40 (m, 2H), 7.42 (d, *J* = 2.8 Hz, 1H), 7.52-7.54 (, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 14.7, 19.9, 69.5, 115.2, 115.4, 124.2, 125.9, 126.0, 126.1, 126.5, 127.4, 128.4, 134.5, 138.8, 140.3, 141.9, 143.8, 161.3

MS (ESI) [M+H]⁺ = 335.0

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.48 min, m/z: 335.0 ([M+H]⁺)

6-methoxy-2-(5-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (49)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-5-methoxy-N-phenylbenzamide (242 mg, 1.0 mmol), 5-methylthiophen-2-carboxaldehyde (110 μ L, 1.007 mmol). The filtration yielded the title compound (312 mg, 89%) as a pale yellow solid.

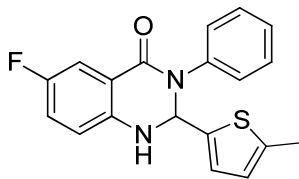
¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 2.31 (s, 3H), 3.72 (s, 3H), 6.36 (d, J = 2.9 Hz, 1H), 6.53-6.56 (m, 1H), 6.71 (d, J = 3.6 Hz, 1H), 6.81 (d, J = 8.7 Hz, 1H), 7.00 (dd, J = 8.8 Hz, J' = 3.0 Hz, 1H), 7.21-7.42 (m, 7H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 14.9, 55.3, 70.0, 110.1, 116.6, 117.4, 122.0, 124.4, 126.2, 126.3, 128.7, 139.1, 140.4, 140.6, 142.1, 152.1, 161.4

MS (ESI) [M+H]⁺ = 351.1

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 6.75 min, m/z : 351.1 ([M+H]⁺)

6-fluoro-2-(5-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (50)



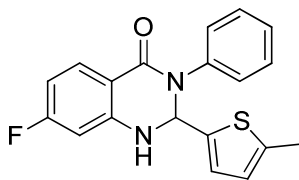
The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-5-fluoro-N-phenylbenzamide (201 mg, 0.873 mmol), 5-methylthiophen-2-carboxaldehyde (96 μ L, 0.879 mmol). The filtration yielded the title compound (206 mg, 70%) as a pale yellow solid.

¹H-NMR (400MHz, DMSO) δ (ppm) = 2.30 (s, 3H), 6.42 (d, *J* = 2.8 Hz, 1H), 6.52-6.55 (m, 1H), 6.71 (d, *J* = 3.4 Hz, 1H), 6.85 (dd, *J* = 9.0 Hz, *J'* = 4.4 Hz, 1H), 7.18-7.47 (m, 6H), 7.59 (d, *J* = 2.8 Hz, 1H), 7.70-7.76 (m, 1H)

MS (ESI) [M+H]⁺ = 339.2

LC/MS (XBridge 100 × 4.6 mm) : *t_R* = 8.52 min, *m/z* : 339.2 ([M+H]⁺)

7-fluoro-2-(5-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (51)



The title compound was prepared following the same general protocol as described for compound **1** using 2-amino-4-fluoro-N-phenylbenzamide (321 mg, 1.394 mmol), 5-methylthiophen-2-carboxaldehyde (153 μL, 1.400 mmol). The filtration yielded the title compound (376 mg, 80%) as a pale yellow solid.

¹H-NMR (400MHz, DMSO-*d*₆) δ (ppm) = 2.32 (s, 3H), 6.46 (d, *J* = 2.8 Hz, 1H), 6.54-6.61 (m, 3H), 6.73 (d, *J* = 3.5 Hz, 1H), 7.22-7.41 (m, 5H), 7.78 (dd, *J* = 8.2 Hz, *J'* = 6.6Hz, 1H), 7.90 (d, *J* = 2.8 Hz, 1H),

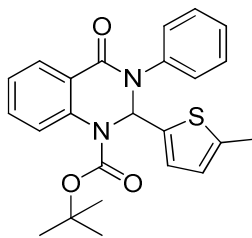
¹³C-NMR (100MHz, DMSO-*d*₆) δ (ppm) = 14.9, 69.6, 100.7, 100.9, 105.4, 105.6, 112.2, 124.5, 126.3, 126.4, 126.5, 128.7, 130.9, 131.0, 139.4, 140.3, 141.7, 148.3, 148.4, 160.7, 164.6, 167.0

MS (ESI) [M+H]⁺ = 339.1

LC/MS (XBridge 100 × 4.6 mm) : *t_R* = 6.97 min, *m/z* : 339.1 ([M+H]⁺)

tert-butyl 2-(5-methylthiophen-2-yl)-4-oxo-3-phenyl-3,4-dihydroquinazoline-1(2H)-carboxylate

(59)



To a solution of **1** (100 mg, 1.0 equiv.), triethylamine (50 μ L, 1.1 equiv.) and DMAP (2 mg, 0.05equiv.) in anhydrous dichloromethane (1.6mL, 0.2M) was added a solution of *tert*-butyldicarbonate (69 mg, 1.0 equiv.) in CH₂Cl₂ (1.0mL). The mixture was then stirred at room temperature under argon for 18h. The mixture was quenched with an aqueous solution of NH₄Cl (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The purification by silica gel chromatography of the crude mixture (EtOAc/heptane 2/8 as eluent) yielded the title compound (110 mg, 84%) as a white solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 1.60 (s, 9H), 2.34 (s, 3H), 6.42-6.45 (m, 1H), 6.74-6.76 (m, 1H), 7.20-7.30 (m, 2H), 7.39-7.73 (m, 7H), 8.11 (dd, J = 1.6 Hz, J' = 7.8 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 15.1, 28.1, 83.3, 123.1, 123.9, 124.4, 124.8, 125.4, 126.7, 126.8, 128.2, 129.0, 132.5, 137.6, 138.5, 140.0, 140.6, 151.4, 161.3

MS (ESI) [M+H]⁺ = 420.8

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 9.65 min, m/z : 420.8 ([M+H⁺])

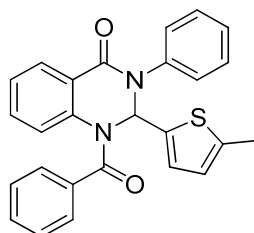
Gradient A : t_R = 23.84 min

Gradient D : t_R = 22.12 min

I.R. (neat, cm⁻¹) 3062, 2979, 2930, 2886, 1707, 1671, 1467, 1328, 1266, 761, 693 \square

HRMS m/z $[(M+H)^+]$ calcd for $C_{24}H_{25}N_2O_3S$ 421.1586 found 421.1586.

1-benzoyl-2-(5-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (60)



To a solution of **1** (100 mg, 1.0 equiv.), triethylamine (50 μ L, 1.1 equiv.) and DMAP (2 mg, 0.05equiv.) in anhydrous dichloromethane (1.6mL, 0.2M) was added benzoyl chloride (44 μ L, 1.2 equiv.). The mixture was then stirred at room temperature under argon for 18h. The mixture was quenched with an aqueous solution of NH_4Cl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The purification by silica gel chromatography of the crude mixture (EtOAc/heptane 3/7 as eluent) yielded the title compound (122 mg, 92%) as an oil.

1H -NMR (400MHz, $CDCl_3$) δ (ppm) = 2.33 (s, 3H), 6.45-6.50 (m, 1H), 6.57 (brs, 1H), 6.84 (d, J = 3.9 Hz, 1H), 7.13-7.50 (m, 10H), 7.53-7.59 (m, 3H), 8.15 (dd, J = 7.6 Hz, J' = 1.8 Hz, 1H)

^{13}C -NMR (100MHz, $CDCl_3$) δ (ppm) = 15.2, 122.7, 124.4, 124.5, 125.5, 125.7, 127.1, 127.3, 128.4, 128.7, 129.1, 129.2, 131.6, 132.2, 133.4, 137.5, 138.0, 139.7, 141.1, 161.4, 168.2

MS (ESI) $[M+H]^+$ = 424.8

LC/MS (XBridge 100 x 4.6 mm) : t_R = 8.83 min, m/z : 424.8 ($[M+H]^+$)

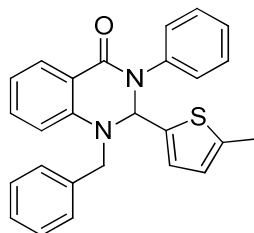
Gradient A : t_R = 22.18 min

Gradient D : t_R = 20.17 min

I.R. (neat, cm^{-1}) 3058, 2982, 2920, 2860, 1667, 1651, 1486, 1372, 1262, 743, 703

HRMS m/z [(M+H)⁺] calcd for $\text{C}_{26}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$ 425.1328 found 425.1324.

1-benzyl-2-(5-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (61)



The title compound was prepared following the general protocol E using NaH (19 mg, 0.475 mmol), **1** (100 mg, 0.312 mmol) and benzylbromide (41 μL , 0.345 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (141 mg, 99%) as a colorless oil.

¹H-NMR (400MHz, CDCl_3) δ (ppm) = 2.35 (s, 3H), 4.29 (d, $J = 15.0$ Hz, 1H), 4.73(d, $J = 15.0$ Hz, 1H), 5.94 (s, 1H), 6.47-6.50 (m, 1H), 6.61 (d, $J = 3.5$ Hz, 1H), 6.86 (d, $J = 8.1$ Hz, 1H), 7.01 (t, $J = 7.6$ Hz, 1H), 7.21-7.50 (m, 11H), 8.16 (dd, $J = 7.6$ Hz, $J' = 1.6$ Hz, 1H)

¹³C-NMR (100MHz, CDCl_3) δ (ppm) = 15.2, 53.2, 74.9, 115.0, 119.3, 120.0, 124.0, 126.2, 126.7, 127.7, 127.8, 128.8, 128.9, 129.0, 133.8, 136.3, 138.1, 140.3, 140.4, 146.1, 161.9

MS (ESI) [(M+H)⁺] = 410.9

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 9.40$ min, m/z : 410.9 [(M+H)⁺]

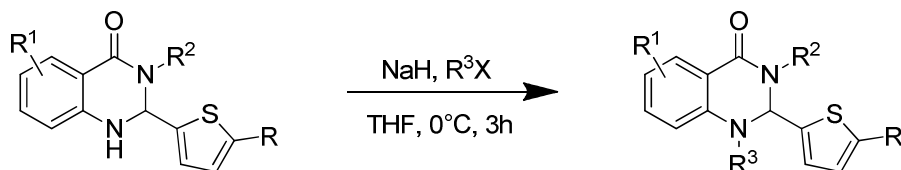
Gradient A : $t_R = 23.71$ min

Gradient D : $t_R = 20.92$ min

I.R. (neat, cm^{-1}) 3063, 2918, 2860, 1660, 1605, 1493, 1228, 750, 695

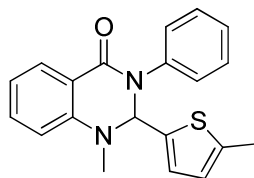
HRMS m/z [(M+H)⁺] calcd for C₂₆H₂₃N₂OS 411.1549 found 411.1531.

General procedure E: Preparation of N-alkyl tetrahydroquinazolin-4-one



To a mixture of NaH (1.5equiv.) in anhydrous THF (0.3M) was added dropwise a solution of analogues of **1** or N-H tetrahydroquinazolin-4-one derivative (1 equiv.) in anhydrous THF (0.5M) at 0 °C. After 30min, alkyl halide (1.1 equiv) was added dropwise. After 10min, the solution was warm to room temperature and stirred for 3h. The reaction was then quenched with a saturated solution of NaHCO₃. The aqueous layer was then repeatedly extracted with CH₂Cl₂. The combined organic layers were then washed with a 1M solution of HCl (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The purification by silica gel chromatography of the crude mixture yielded the expected compound as a solid.

1-methyl-2-(5-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (62)



The title compound was prepared following the general protocol E using NaH (19 mg, 0.475 mmol), **1** (100 mg, 0.312 mmol) and iodomethane (21 μ L, 0.337 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (89 mg, 85%) as a white solid.

¹H-NMR (400MHz, DMSO) δ (ppm) = 2.34 (s, 3H), 2.93 (s, 3H), 5.91 (s, 1H), 6.50 (d, J = 2.4Hz, 1H), 6.64-6.67 (m, 2H), 6.96 (t, J = 7.6Hz, 1H), 7.25-7.39 (m, 5H), 7.42-7.47 (m, 1H), 8.11 (dd, J = 1.6Hz, J' = 7.6Hz, 1H)

¹³C-NMR (100MHz, DMSO) δ (ppm) = 15.2, 35.9, 77.9, 112.8, 117.5, 119.0, 124.0, 126.6, 126.7, 126.9, 128.9, 128.9, 134.0, 137.0, 140.3, 140.5, 146.3, 161.8

MS (ESI) [M+H]⁺ = 334.9

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 8.20 min, m/z : 334.9 ([M+H⁺])

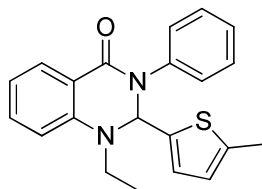
Gradient A : t_R = 21.15 min

Gradient D : t_R = 17.99 min

I.R. (neat, cm⁻¹) 3063, 2915, 2856, 1670, 1608, 1531, 1468, 1226, 761, 693

HRMS m/z [(M+H)⁺] calcd for C₂₀H₁₉N₂OS 335.1204 found 335.1218.

1-ethyl-2-(5-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (63)



The title compound was prepared following the general protocol E using NaH (19 mg, 0.475 mmol), **1** (100 mg, 0.312 mmol) and iodoethane (28 μ L, 0.350 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (92 mg, 85%) as a white solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 1.32 (t, *J* = 7.1 Hz, 3H), 2.34 (s, 3H), 3.29 (sex, *J* = 7.1 Hz, 1H), 3.59 (sex, *J* = 7.1 Hz, 1H), 6.04 (s, 1H), 6.46-6.49 (m, 1H), 6.68 (d, *J* = 3.5 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.95 (t, *J* = 7.3 Hz, 1H), 7.23-7.39 (m, 1H), 7.34-7.46 (m, 5H), 8.08 (dd, *J* = 7.8 Hz, *J*' = 1.7 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 13.5, 15.4, 45.0, 75.6, 114.9, 119.2, 119.6, 124.3, 126.2, 126.6, 126.8, 129.2, 129.3, 133.9, 139.7, 140.4, 140.9, 145.9, 162.2

MS (ESI) [M+H]⁺ = 349.1

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.53 min, m/z : 349.1 ([M+H⁺])

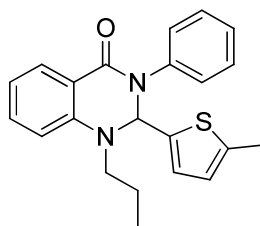
Gradient A : t_R = 22.25 min

Gradient D : t_R = 18.97 min

I.R. (neat, cm⁻¹) 3062, 2977, 2870, 1655, 1605, 1493, 1467, 747, 694

HRMS m/z [(M+H)⁺] calcd for C₂₁H₂₁N₂OS 349.1372 found 349.1375.

2-(5-methylthiophen-2-yl)-3-phenyl-1-propyl-2,3-dihydroquinazolin-4(1H)-one (64)



The title compound was prepared following the general protocol E using NaH (19 mg, 0.475 mmol), **1** (100 mg, 0.312 mmol) and 1-iodopropane (34 μL, 0.349 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (83 mg, 73%) as a white solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 1.05 (t, *J* = 7.3 Hz, 3H), 1.65-1.84 (m, 2H), 2.34 (s, 3H), 3.07-3.17 (m, 1H), 3.49-3.59 (m, 1H), 6.00 (s, 1H), 6.46-6.49 (m, 1H), 6.67 (d, *J* = 3.5 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.93 (t, *J* = 7.3 Hz, 1H), 7.25-7.30 (m, 1H), 7.34-7.46 (m, 5H), 8.08 (dd, *J* = 7.8 Hz, *J*' = 1.7 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 11.6, 15.4, 21.3, 52.1, 76.1, 114.6, 118.9, 119.3, 124.3, 126.2, 126.6, 126.8, 129.2, 129.3, 133.9, 139.6, 140.3, 140.9, 146.1, 162.3

MS (ESI) [M+H]⁺ = 363.1

LC/MS (XBridge 100 × 4.6 mm) : t_R = 9.12 min, m/z : 363.1 ([M+H⁺])

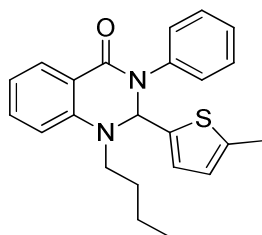
Gradient A : t_R = 23.32 min

Gradient D : t_R = 20.17 min

I.R. (neat, cm⁻¹) 3065, 2962, 2873, 1655, 1606, 1492, 1467, 750, 694

HRMS *m/z* [(M+H)⁺] calcd for C₂₂H₂₃N₂OS 363.1529 found 363.1531.

1-butyl-2-(5-methylthiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (65)



The title compound was prepared following the general protocol E using NaH (19 mg, 0.475 mmol), **1** (100 mg, 0.312 mmol) and 1-iodobutane (39 μL, 0.343 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 2/8) yielded the title compound (87 mg, 74%) as a white solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 0.99 (t, *J* = 7.3 Hz, 3H), 1.38-1.57 (m, 2H), 1.61-1.81 (m, 2H), 2.34 (s, 3H), 3.12-3.21 (m, 1H), 3.51-3.61 (m, 1H), 6.00 (m, 1H), 6.46-6.49 (m, 1H), 6.67 (d, *J* = 3.5 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.93 (t, *J* = 7.3 Hz, 1H), 7.25-7.31 (m, 1H), 7.34-7.46 (m, 5H), 8.08 (dd, *J* = 7.8 Hz, *J'* = 1.6 Hz, 1H),

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 14.0, 15.4, 20.3, 30.1, 50.1, 76.1, 114.6, 119.0, 119.3, 124.3, 126.2, 126.6, 126.8, 129.2, 129.3, 133.9, 139.6, 140.3, 140.9, 146.1, 162.2

MS (ESI) [M+H]⁺ = 377.2

LC/MS (XBridge 100 × 4.6 mm) : t_R = 9.47 min, m/z : 377.2 ([M+H⁺])

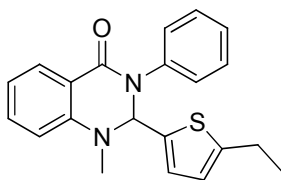
Gradient A : t_R = 24.59 min

Gradient D : t_R = 21.37 min

I.R. (neat, cm⁻¹) 3068, 2957, 2871, 1656, 1605, 1492, 748, 694

HRMS *m/z* [(M+H)⁺] calcd for C₂₃H₂₅N₂OS 377.1671 found 377.1688.

2-(5-ethylthiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (66)



The title compound was prepared following the general protocol E using NaH (15 mg, 0.375 mmol), **17** (100 mg, 0.299 mmol) and iodomethane (20 μL, 0.321 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (87 mg, 84%) as a white solid

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 1.21 (t, *J* = 7.5 Hz, 3H), 2.70 (q, *J* = 7.5 Hz, 2H), 2.94 (s, 3H), 5.92 (s, 1H), 6.51-6.54 (m, 1H), 6.65-.68 (m, 2H), 6.95 (t, *J* = 8.1 Hz, 1H), 7.24-7.47 (m, 6H), 8.10 (dd, *J* = 7.7 Hz, *J'* = 1.6 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 15.5, 23.4, 36.2, 78.2, 113.0, 117.7, 119.2, 122.3, 126.7, 126.8, 127.1, 129.1, 129.2, 134.2, 136.9, 140.7, 146.5, 162.0

MS (ESI) [M+H]⁺ = 349.1

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.77 min, m/z : 349.1 ([M+H⁺])

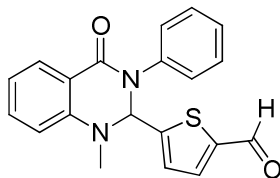
Gradient A : t_R = 21.95 min

Gradient D : t_R = 19.02 min

I.R. (neat, cm⁻¹) 3068, 2968, 2863, 1655, 1605, 1495, 749, 694

HRMS m/z [(M+H)⁺] calcd for C₂₁H₂₁N₂OS 349.1373 found 349.1375.

5-(1-methyl-4-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)thiophene-2-carbaldehyde (67)



¹H-NMR (400MHz, CDCl₃) δ (ppm) = 2.92 (s, 3H), 6.00 (s, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.87-6.92 (m, 2H), 7.17-7.39 (m, 6H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.99 (dd, *J* = 7.8 Hz, *J'* = 1.6 Hz, 1H), 9.69 (s, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 36.8, 77.6, 113.8, 117.9, 120.1, 126.5, 127.3, 127.6, 129.3, 129.4, 134.5, 135.6, 140.2, 143.5, 145.9, 150.2, 161.6, 182.9

MS (ESI) [M+H]⁺ = 349.1

LC/MS (XBridge 100 × 4.6 mm) :

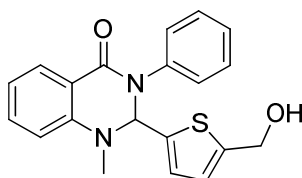
Gradient C : $t_R = 22.25$ min

Gradient F : $t_R = 17.70$ min

I.R. (neat, cm^{-1}) 3071, 2956, 2888, 2810, 1659, 1606, 1494, 750, 695

HRMS m/z [(M+H)⁺] calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$ 349.0995 found 349.1011.

2-(5-(hydroxymethyl)thiophen-2-yl)-1-methyl-3-phenyl-2,3 dihydroquinazolin-4(1H)-one (68)



67 (450 mg, 1.17 mmol) was dissolved in THF/ethanol (9mL, 2:1) and treated with sodium borohydride (221 mg, 5.84 mmol) for 3h. A saturated solution of NaHCO_3 (50 mL) was added and the mixture was stirred 30min. The aqueous layer was extracted with EtOAc (3 x 30mL). The combined extracts were dried over Na_2SO_4 , filtered and concentrated in vacuo. The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 5/5) yielded the title compound (410 mg, 100%) as a white solid.

¹H-NMR (400MHz, DMSO- d_6) δ (ppm) = 2.94 (s, 3H), 4.48 (d, $J = 4.9$ Hz, 2H), 5.40 (t, $J = 5.9$ Hz, 1H), 6.42 (s, 1H), 6.72 (d, $J = 3.6$ Hz, 1H), 6.75 (d, $J = 8.2$ Hz, 1H), 6.81 (d, $J = 3.6$ Hz, 1H), 6.91 (t, $J = 7.4$ Hz, 1H), 7.25-7.33 (m, 3H), 7.37-7.49 (m, 3H), 7.86 (dd, $J = 7.8$ Hz, $J' = 1.6$ Hz, 1H)

¹³C-NMR (100MHz, DMSO- d_6) δ (ppm) = 35.0, 58.2, 75.9, 113.2, 116.9, 118.5, 122.8, 126.5, 126.6, 126.7, 128.2, 128.8, 134.3, 138.3, 140.2, 146.5, 146.6, 160.8

MS (ESI) [M+H]⁺ = 351.1

LC/MS (XBridge 100 × 4.6 mm) :

Gradient C : $t_R = 21.85$ min

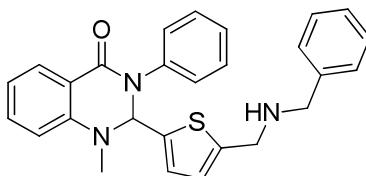
Gradient G : $t_R = 19.22$ min

I.R. (neat, cm^{-1}) 3424, 3064, 2922, 2887, 1634, 1597, 1492, 748, 695

HRMS m/z $[(M+H)^+]$ calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$ 351.1165 found 351.1167.

2-(5-((benzylamino)methyl)thiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one

(69)



To a solution of **67** (71 mg, 0.204 mmol), benzylamine (23 μL , 0.211 mmol) and acetic acid (60 μL , 1.070 mmol) in methanol/THF (3 mL, 1:1) was added sodium cyanoborohydride (20 mg, 0.318 mmol). After stirring for 19h, the mixture was quenched with an aqueous solution of NaHCO_3 (10 mL) and the organic solvent was removed under reduced pressure. The aqueous layer was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 6/4) yielded the title compound (65 mg, 72%) as a pale yellow solid.

$^1\text{H-NMR}$ (400MHz, DMSO-d_6) δ (ppm) = 2.94 (s, 3H), 3.60 (s, 2H), 3.68 (s, 2H), 6.40 (s, 1H), 6.70 (d, $J = 3.6$ Hz, 1H), 6.75 (d, $J = 8.1$ Hz, 1H), 6.79 (d, $J = 3.6$ Hz, 1H), 6.91 (t, $J = 7.4$ Hz, 1H), 7.18-7.32 (m, 8H), 7.38-7.50 (m, 3H), 7.86 (dd, $J = 7.8$ Hz, $J' = 1.6$ Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO-d_6) δ (ppm) = 35.5, 47.4, 52.4, 76.4, 113.5, 117.3, 118.8, 123.7, 126.9, 127.0, 127.1, 128.4, 128.5, 128.6, 129.2, 134.7, 138.3, 140.6, 140.7, 146.0, 147.0, 161.3

I.R. (neat, cm^{-1}) 3323, 3061, 3028, 2883, 2823, 1658, 1606, 1494, 750, 696

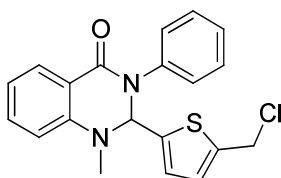
LC/MS (XBridge 100 \times 4.6 mm) :

Gradient C : $t_R = 20.32$ min

Gradient G : $t_R = 19.07$ min

HRMS m/z [(M+H) $^+$] calcd for $\text{C}_{27}\text{H}_{26}\text{N}_3\text{OS}$ 440.1783 found 440.1797.

2-(5-(chloromethyl)thiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (70)



68 (70 mg, 0.200 mmol) in anhydrous dichloromethane was treated with thionyl chloride (73 μ L, 1.005 mmol) at 0 $^\circ$ C. The mixture was warmed up naturally to room temperature and stirred for 16h. The mixture was then concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (20mL) and a saturated solution of NaHCO_3 (10mL). The organic layer was washed with water (10mL) and brine (10mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 3/7) yielded the title compound (24 mg, 33%) as a white solid.

$^1\text{H-NMR}$ (400MHz, DMSO-d_6) δ (ppm) = 2.96 (s, 3H), 4.89 (s, 2H), 6.48 (s, 1H), 6.78 (d, $J = 8.1$ Hz, 1H), 6.85 (d, $J = 3.6$ Hz, 1H), 6.92 (t, $J = 8.1$ Hz, 1H), 6.97 (d, $J = 3.6$ Hz, 1H), 7.26-7.33 (m, 3H), 7.38-7.44 (m, 2H), 7.45-7.50 (m, 1H), 7.86 (dd, $J = 7.8$ Hz, $J' = 1.7$ Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO-d_6) δ (ppm) = 35.1, 40.4, 75.7, 113.3, 116.8, 118.7, 126.4, 126.7, 127.0, 127.3, 128.2, 128.9, 134.4, 140.0, 140.2, 141.2, 146.4, 160.8

MS (ESI) [(M+H) $^+$] = 369.1

LC/MS (XBridge 100 × 4.6 mm) :

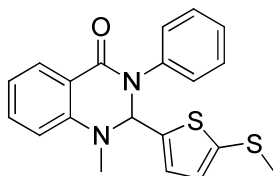
Gradient A : $t_R = 20.32$ min

Gradient D : $t_R = 17.52$ min

I.R. (neat, cm^{-1}) 3069, 2924, 2851, 1651, 1605, 1495, 749, 695

HRMS m/z [(M+H)⁺] calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{OS}^{35}\text{Cl}$ 369.0824 found 369.0828.

1-methyl-2-(5-(methylthio)thiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (71)



The title compound was prepared following the general protocol E using NaH (14 mg, 0.350 mmol), **20** (100 mg, 0.284 mmol) and iodomethane (19 μL , 0.305 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (95 mg, 91%) as a white solid.

¹H-NMR (400MHz, CDCl_3) δ (ppm) = 2.39 (s, 3H), 2.95 (s, 3H), 5.91 (s, 1H), 6.64-6.70 (m, 2H), 6.77 (d, $J = 3.5$ Hz, 1H), 6.96 (t, $J = 7.6$ Hz, 1H), 7.25-7.36 (m, 3H), 7.34-7.40 (m, 2H), 7.41-7.47 (m, 1H), 8.08 (dd, $J = 7.8$ Hz, $J' = 1.5$ Hz, 1H)

¹³C-NMR (100MHz, CDCl_3) δ (ppm) = 21.4, 36.3, 78.1, 113.3, 117.7, 119.5, 126.7, 127.2, 129.1, 129.2, 134.3, 138.3, 140.5, 141.5, 146.3, 161.9

MS (ESI) [M+H]⁺ = 367.1

LC/MS (XBridge 100 × 4.6 mm) : $t_R = 8.67$ min, m/z : 367.1 ([M+H]⁺)

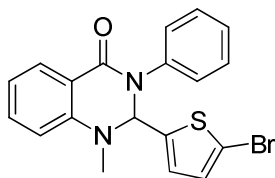
Gradient A : $t_R = 21.67$ min

Gradient D : $t_R = 19.62$ min

I.R. (neat, cm^{-1}) 3068, 2958, 2884, 1654, 1605, 1492, 750, 694

HRMS m/z [(M+H)⁺] calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{OS}$ 367.0952 found 367.0939.

2-(5-bromothiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (72)



The title compound was prepared following the general protocol E using NaH (371 mg, 9.28 mmol), **19** (2.97g, 7.73 mmol) and iodomethane (530 μL , 8.51 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 4/6) yielded the title compound (2.67 mg, 87%) as a pale yellow solid.

¹H-NMR (400MHz, CDCl_3) δ (ppm) = 2.95 (s, 3H), 5.90 (s, 1H), 6.61 (d, $J = 3.6$ Hz, 1H), 6.69 (d, $J = 8.2$ Hz, 1H), 6.80 (d, $J = 3.6$ Hz, 1H), 6.99 (t, $J = 7.5$ Hz, 1H), 7.24-7.33 (m, 3H), 7.34-7.42 (m, 2H), 7.43-7.47 (t, $J = 7.5$ Hz, 1H), 8.08 (d, $J = 7.5$ Hz, 1H)

¹³C-NMR (100MHz, CDCl_3) δ (ppm) = 36.5, 78.2, 112.7, 113.6, 117.8, 119.9, 126.8, 127.3, 127.4, 129.0, 129.4, 134.5, 140.4, 141.5, 146.3, 161.7

MS (ESI) [M+H]⁺ = 398.6, 400.6

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 8.87$ min, m/z : 398.6, 400.6 ([M+H⁺])

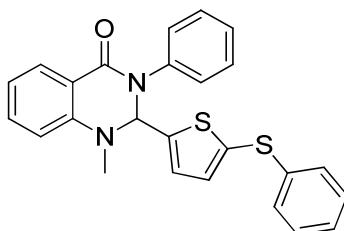
Gradient A : $t_R = 22.02$ min

Gradient D : $t_R = 19.34$ min

I.R. (neat, cm^{-1}) 3071, 2953, 2886, 1651, 1605, 1493, 748, 695

HRMS m/z $[(M+H)^+]$ calcd for $C_{19}H_{16}N_2OSBr$ 399.0169 found 399.0167.

1-methyl-3-phenyl-2-(5-(phenylthio)thiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (73)



A mixture of **72** (70 mg, 0.175 mmol), thiophenol (18 μ L, 0.175 mmol), Tris(dibenzylideneacetone)dipalladium(0) (16 mg, 0.017 mmol), 1,1'-Bis(diphenylphosphino)ferrocene (15 mg, 0.027 mmol) and KO t -Bu (39 mg, 0.348 mmol) in degassed anhydrous dioxane was sealed in a tube under argon. The mixture was stirred at 140 °C for 1h under microwave. The reaction was quenched with brine (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 \times 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (36 mg, 48%) as a pale yellow solid.

1H -NMR (400MHz, $CDCl_3$) δ (ppm) = 2.98 (s, 3H), 5.96 (s, 1H), 6.69 (d, J = 8.1Hz, 1H), 6.81 (d, J = 3.7 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 3.7 Hz, 1H), 7.10-7.19 (m, 3H), 7.20-7.27 (m, 2H), 7.27-7.34 (m, 3H), 7.35-7.47 (m, 3H), 8.07 (dd, J = 7.8 Hz, J' = 1.6 Hz, 1H).

^{13}C -NMR (100MHz, $CDCl_3$) δ (ppm) = 36.7, 78.1, 113.5, 117.9, 119.8, 126.5, 126.8, 127.3, 127.5, 127.5, 129.1, 129.3, 129.4, 134.4, 134.9, 137.8, 140.5, 145.4, 146.3, 161.9

MS (ESI) $[M+H]^+$ = 428.9

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 9.82 min, m/z : 428.9 ($[M+H]^+$)

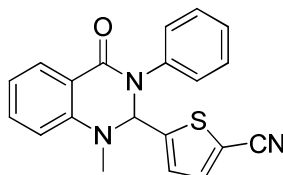
Gradient A : t_R = 23.87 min

Gradient D : t_R = 21.60 min

I.R. (neat, cm⁻¹) 3061, 2928, 2860, 1659, 1605, 1494, 748, 693

HRMS *m/z* [(M+H)⁺] calcd for C₂₅H₂₁N₂OS₂ 429.1111 found 429.1095.

5-(1-methyl-4-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)thiophene-2-carbonitrile (74)



A mixture of **72** (500 mg, 1.25 mmol), zinc cyanide (148 mg, 1.26 mmol) and tris(dibenzylideneacetone)dipalladium (0) (57 mg, 0.06 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (70 mg, 0.13 mmol) in degassed anhydrous DMF (4.1mL, 0.3M) was stirred at 150 °C for 1h under microwave. The reaction mixture was partitioned between a saturated solution of NaHCO₃ (30mL) and EtOAc (50mL). The aqueous layer was extracted with additional EtOAc (3 x 30 mL). The combined extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (292 mg, 68%) as a pale brown solid.

¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 2.98 (s, 3H), 6.68 (s, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 3.8 Hz, 1H), 7.28-7.34 (m, 3H), 7.40-7.46 (m, 2H), 7.48-7.54 (m, 1H), 7.78 (d, *J* = 3.8 Hz, 1H), 7.88 (dd, *J* = 7.7 Hz, *J'* = 1.6 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 35.2, 75.0, 107.8, 113.7, 113.9, 116.8, 119.4, 126.6, 127.0, 128.0, 129.0, 134.7, 138.5, 139.6, 146.1, 148.0, 160.5

MS (ESI) [M+H]⁺ = 346.0

LC/MS (XBridge 100 × 4.6 mm) : t_R = 7.88 min, m/z : 346.0 ([M+H⁺])

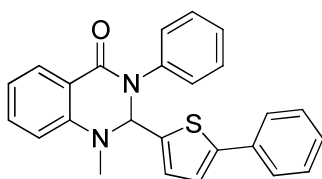
Gradient B : $t_R = 20.67$ min

Gradient E : $t_R = 17.37$ min

I.R. (neat, cm^{-1}) 3073, 2958, 2887, 2219, 1656, 1606, 1492, 749, 695

HRMS m/z $[(M+H)^+]$ calcd for $\text{C}_{20}\text{H}_{16}\text{N}_3\text{OS}$ 346.1003 found 346.1014.

1-methyl-3-phenyl-2-(5-phenylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (75)



The title compound was prepared following the general protocol E using NaH (13 mg, 0.325 mmol), **21** (100 mg, 0.261 mmol) and iodomethane (18 μL , 0.289 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (89 mg, 69%) as a white solid.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ (ppm) = 3.00 (s, 3H), 5.99 (s, 1H), 6.68 (d, $J = 8.1\text{Hz}$, 1H), 6.84 (d, $J = 3.5\text{ Hz}$, 1H), 6.98 (t, $J = 7.6\text{ Hz}$, 1H), 7.06 (d, $J = 3.7\text{ Hz}$, 1H), 7.21-7.50 (m, 11H), 8.14 (dd, $J = 7.8\text{ Hz}$, $J = 1.6\text{ Hz}$, 1H)

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ (ppm) = 36.4, 78.1, 113.3, 117.8, 119.5, 122.1, 125.9, 126.8, 127.3, 127.8, 127.9, 128.9, 129.3, 129.3, 133.7, 134.3, 139.1, 140.6, 144.8, 146.4, 162.0

MS (ESI) $[(M+H)^+]$ = 397.2

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 9.25$ min, m/z : 397.2 ($[(M+H)^+]$)

Gradient A : $t_R = 23.14$ min

Gradient D : $t_R = 20.22$ min

I.R. (neat, cm^{-1}) 3061, 2918, 2886, 1656, 1605, 1494, 752, 694 \square

HRMS m/z $[(M+H)^+]$ calcd for $\text{C}_{25}\text{H}_{21}\text{N}_2\text{OS}$ 397.1386 found 397.1375.

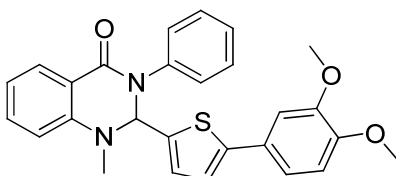
GENERAL PROCEDURE F: Suzuki



A mixture of **72** (1.0 equiv), boronic acid (1.1 equiv), tetrakis(triphenylphosphine)palladium (0) (0.08 equiv) and potassium carbonate (2 equiv) in dimethoxyethane / water (10:1, 0.1M) was stirred at 110°C for 1h under microwave in a sealed tube. The reaction was quenched with a saturated solution of NaHCO_3 . The aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO_4 , filtered and concentrated in *vacuo*. The purification by silica gel chromatography of the crude mixture yielded the expected compound.

2-(5-(3,4-dimethoxyphenyl)thiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one

(76)



The title compound was prepared following the general protocol F using **72** (70 mg, 0.175 mmol), 3,4-dimethoxyphenylboronic acid (35 mg, 0.192 mmol), $\text{Pd(PPh}_3)_4$ (16 mg, 0.014 mmol) and potassium

carbonate (48 mg, 0.374 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 5/5) yielded the title compound (70 mg, 88%) as a pale yellow solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 2.99 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 5.97 (s, 1H), 6.67 (d, *J* = 8.1Hz, 1H), 6.80 (d, *J* = 5.1 Hz, 1H), 6.81 (s, 2H), 6.92-6.97 (m, 2H), 7.00-7.05 (s, 1H), 7.25-7.40 (m, 6H), 8.12 (dd, *J* = 7.8 Hz, *J'* = 1.6 Hz, 1H).

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 36.3, 56.0, 78.1, 109.2, 11.4, 113.2, 117.6, 118.7, 119.4, 121.3, 126.8, 126.9, 127.3, 127.8, 128.6, 128.7, 129.3, 132.2, 134.4, 138.1, 140.5, 144.9, 146.4, 149.0, 149.1, 162.1

MS (ESI) [M+H]⁺ = 457.2

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.20 min, m/z : 457.2 ([M+H⁺])

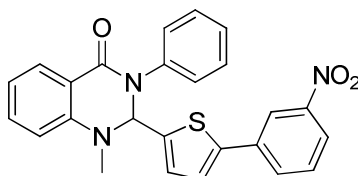
Gradient A : t_R = 21.74 min

Gradient D : t_R = 18.22 min

I.R. (neat, cm⁻¹) 3061, 2956, 2839, 1656, 1603, 1513, 1257, 1141, 1025, 750, 694

HRMS m/z [(M+H)⁺] calcd for C₂₇H₂₅N₂O₃S 457.1592 found 457.1586.

1-methyl-2-(5-(3-nitrophenyl)thiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (77)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), 3-nitrophenylboronic acid (46 mg, 0.276 mmol), Pd(PPh₃)₄ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 5/5) yielded the title compound (99 mg, 90%) as a pale yellow solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 3.00 (s, 3H), 6.04 (s, 1H), 6.70 (d, *J* = 8.1Hz, 1H), 6.88 (d, *J* = 3.8 Hz, 1H), 6.97 (t, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 3.8 Hz, 1H), 7.25-7.30 (m, 1H), 7.32-7.41 (m, 3H), 7.41-7.48 (m, 2H), 7.63-7.73 (m, 2H), 8.04 (ddd, *J* = 8.1 Hz, *J*' = 2.3 Hz, *J*'' = 0.9 Hz, 1H), 8.11 (dd, *J* = 7.8 Hz, *J*' = 1.6 Hz, 1H), 8.27 (t, *J* = 2.0 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 36.4, 77.9, 113.4, 117.7, 119.7, 120.3, 122.2, 123.9, 126.6, 127.3, 128.1, 128.5, 128.6, 129.3, 129.9, 131.5, 132.0, 132.0, 132.1, 134.4, 135.4, 140.4, 141.1, 141.6, 146.2, 148.6, 161.8

MS (ESI) [M+H]⁺ = 442.1

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.70 min, m/z : 442.1 ([M+H]⁺)

Gradient A : t_R = 23.25 min

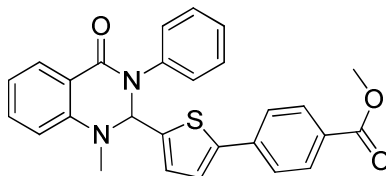
Gradient D : t_R = 19.84 min

I.R. (neat, cm⁻¹) 3069, 2956, 2885, 1656, 1605, 1526, 1493, 1349, 749, 694

HRMS *m/z* [(M+H)⁺] calcd for C₂₅H₁₉N₃O₃S 442.1208 found 442.1225.

methyl 4-(5-(1-methyl-4-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)thiophen-2-yl)benzoate

(78)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), 4-(methoxycarbonyl)phenylboronic acid (50 mg, 0.278 mmol), Pd(PPh₃)₄ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 4/6) yielded the title compound (91 mg, 80%) as a pale yellow solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 2.99 (s, 3H), 3.89 (s, 3H), 6.01 (s, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 3.8 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 3.8 Hz, 1H), 7.25-7.41 (m, 5H), 7.42-7.47 (m, 1H), 7.48-7.53 (m, 2H), 7.95-7.99 (m, 2H), 8.12 (dd, *J* = 7.8 Hz, *J'* = 1.6 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 36.4, 52.2, 78.0, 113.3, 117.7, 119.6, 123.6, 125.5, 126.7, 127.3, 128.0, 129.1, 129.3, 130.2, 134.4, 137.9, 140.5, 140.7, 143.3, 146.3, 161.9, 166.6

MS (ESI) [M+H]⁺ = 455.2

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.70 min, m/z : 455.2 ([M+H]⁺)

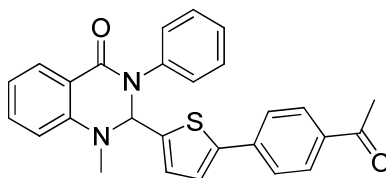
Gradient A : t_R = 23.62 min

Gradient D : t_R = 19.50 min

I.R. (neat, cm⁻¹) 3067, 2950, 2888, 1718, 1658, 1605, 1494, 1279, 768, 750, 695

HRMS *m/z* [(M+H)⁺] calcd for C₂₇H₂₃N₂O₃S 455.1433 found 455.1429.

2-(5-(4-acetylphenyl)thiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (79)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), 4-acetylphenylboronic acid (45 mg, 0.274 mmol), Pd(PPh₃)₄ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 5/5) yielded the title compound (98 mg, 89%) as a pale yellow solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 2.56 (s, 3H), 3.00 (s, 3H), 6.02 (s, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 3.7 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 3.7 Hz, 1H), 7.25-7.30 (m, 1H), 7.32-7.41 (m, 4H), 7.42-7.47 (m, 1H), 7.50-7.54 (m, 2H), 7.86-7.91 (m, 2H), 8.12 (dd, *J* = 7.8 Hz, *J*' = 1.6 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 26.6, 36.4, 77.9, 113.3, 117.7, 119.6, 123.7, 125.6, 126.6, 127.2, 128.0, 129.1, 129.3, 134.4, 136.0, 138.0, 140.5, 140.9, 143.1, 146.2, 161.9

MS (ESI) [M+H]⁺ = 439.2

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.20 min, m/z : 439.2 ([M+H]⁺)

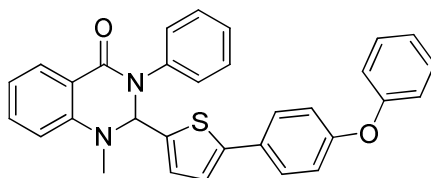
Gradient A : t_R = 21.94 min

Gradient D : t_R = 18.17 min

I.R. (neat, cm⁻¹) 3064, 2958, 2886, 1677, 1658, 1602, 1494, 1267, 750, 695

HRMS *m/z* [(M+H)⁺] calcd for C₂₇H₂₃N₂O₂S 439.1471 found 439.1480.

1-methyl-2-(5-(4-phenoxyphenyl)thiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (80)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), 4-phenoxyphenylboronic acid (59 mg, 0.276 mmol), Pd(PPh₃)₄ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (116 mg, 95%) as a pale yellow solid.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ (ppm) = 2.99 (s, 3H), 5.99 (s, 1H), 6.70 (d, $J = 8.1$ Hz, 1H), 6.83 (d, $J = 3.6$ Hz, 1H), 6.95-7.04 (m, 5H), 7.09-7.16 (m, 2H), 7.27-7.50 (m, 10H), 8.14 (dd, $J = 7.8$ Hz, $J' = 1.6$ Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ (ppm) = 36.3, 78.1, 113.2, 117.6, 117.7, 119.0, 119.1, 119.5, 119.9, 121.6, 123.6, 124.1, 126.8, 127.3, 127.9, 128.9, 129.3, 129.4, 129.9, 130.0, 134.4, 137.7, 138.6, 140.6, 144.3, 146.4, 156.9, 157.2

$\text{MS (ESI) [M+H]^+} = 489.1$

$\text{LC/MS (XBridge 100} \times 4.6 \text{ mm)}$: $t_{\text{R}} = 9.92$ min, m/z : 489.1 ($[\text{M+H}^+]$)

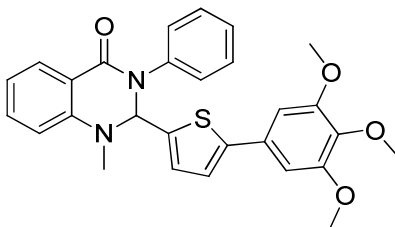
Gradient A : $t_{\text{R}} = 25.05$ min

Gradient D : $t_{\text{R}} = 23.09$ min

$\text{I.R. (neat, cm}^{-1}\text{)}$ 3065, 3039, 2926, 2885, 1658, 1604, 1589, 1490, 1227, 750, 693

$\text{HRMS } m/z$ $[\text{M+H}^+]$ calcd for $\text{C}_{31}\text{H}_{25}\text{N}_2\text{O}_2\text{S}$ 489.1643 found 489.1637.

1-methyl-3-phenyl-2-(5-(3,4,5-trimethoxyphenyl)thiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (81)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), 3,4,5-trimethoxybenzeneboronic acid (58 mg, 0.274 mmol), $\text{Pd(PPh}_3)_4$ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 5/5) yielded the title compound (89 mg, 73%) as a pale yellow solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 2.99 (s, 3H), 3.84 (s, 3H), 3.86 (s, 6H), 5.99 (s, 1H), 6.66 (s, 2H), 6.83 (d, *J* = 3.7 Hz, 1H), 6.93-6.98 (m, 1H), 6.98 (d, *J* = 3.7 Hz, 1H), 7.24-7.47 (m, 7H), 8.12 (dd, *J* = 7.8 Hz, *J'* = 1.6 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 36.3, 56.3, 61.0, 78.0, 103.4, 113.2, 117.6, 119.4, 122.1, 126.7, 127.3, 127.7, 127.9, 129.2, 129.3, 129.6, 134.4, 138.1, 139.0, 140.5, 144.8, 146.3, 153.5, 162.0

MS (ESI) [M+H]⁺ = 487.2

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.23 min, m/z : 487.2 ([M+H⁺])

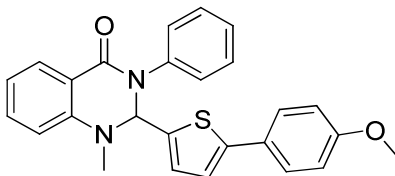
Gradient A : t_R = 21.85 min

Gradient D : t_R = 18.25 min

I.R. (neat, cm⁻¹) 3062, 2937, 2834, 1658, 1603, 1582, 1495, 1242, 1126, 749, 695

HRMS *m/z* [(M+H)⁺] calcd for C₂₈H₂₇N₂O₄S 487.1710 found 487.1692.

2-(5-(4-methoxyphenyl)thiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (82)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), 4-methoxybenzeneboronic acid (42 mg, 0.276 mmol), Pd(PPh₃)₄ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 4/6) yielded the title compound (75 mg, 70%) as a white solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 2.98 (s, 3H), 3.79 (s, 3H), 5.98 (s, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 3.7 Hz, 1H), 6.83-6.87 (m, 2H), 6.94 (d, *J* = 3.7 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 7.01-7.05 (m, 2H), 7.33-7.43 (m, 6H), 8.14 (dd, *J* = 7.8 Hz, *J'* = 1.6 Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ (ppm) = 36.2, 55.2, 55.4, 78.1, 113.2, 113.6, 114.3, 117.6, 119.4, 120.9, 126.5, 126.8, 127.1, 127.3, 127.8, 129.3, 134.4, 135.9, 137.5, 137.8, 140.6, 144.8, 146.4, 159.5, 162.1, 163.2

$\text{MS (ESI) } [M+H]^+ = 427.1$

$\text{LC/MS (XBridge 100} \times 4.6 \text{ mm)} : t_R = 8.80 \text{ min, } m/z : 427.1 ([M+H]^+)$

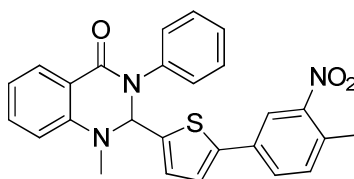
Gradient A : $t_R = 23.52 \text{ min}$

Gradient D : $t_R = 19.77 \text{ min}$

$\text{I.R. (neat, cm}^{-1}\text{)} 3067, 2957, 2837, 1656, 1603, 1509, 1493, 1249, 1172, 749, 693$

$\text{HRMS } m/z [(M+H)^+]$ calcd for $\text{C}_{26}\text{H}_{23}\text{N}_2\text{O}_2\text{S}$ 427.1462 found 427.1480.

1-methyl-2-(5-(4-methyl-3-nitrophenyl)thiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (83)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), 4-methyl-3-nitrophenylboronic acid (50 mg, 0.276 mmol), $\text{Pd(PPh}_3)_4$ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 4/6) yielded the title compound (87 mg, 76%) as a brown solid.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ (ppm) = 2.54 (s, 3H), 2.99 (s, 3H), 6.02 (s, 1H), 6.70 (d, $J = 8.1 \text{ Hz}$, 1H), 6.85 (d, $J = 3.8 \text{ Hz}$, 1H), 6.97 (t, $J = 7.5 \text{ Hz}$, 1H), 7.09 (d, $J = 3.8 \text{ Hz}$, 1H), 7.22-7.54 (m, 8H), 8.02 (d, $J = 2.0 \text{ Hz}$, 1H), 8.11 (dd, $J = 7.8 \text{ Hz}$, $J' = 1.6 \text{ Hz}$, 1H)

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ (ppm) = 20.2, 36.5, 78.0, 113.4, 117.8, 119.7, 121.5, 123.4, 126.7, 127.3, 128.0, 129.3, 129.9, 132.6, 133.0, 133.4, 134.4, 140.5, 140.6, 141.8, 146.2, 149.5, 161.9

MS (ESI) $[\text{M}+\text{H}]^+ = 533.9$

$\text{LC/MS (XBridge 100} \times 4.6 \text{ mm)}$: $t_{\text{R}} = 9.67$ min, m/z : 533.9 ($[\text{M}+\text{H}]^+$)

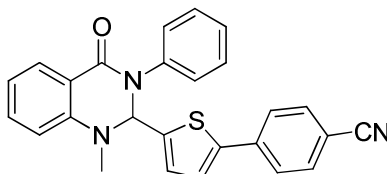
Gradient A : $t_{\text{R}} = 23.89$ min

Gradient D : $t_{\text{R}} = 20.35$ min

$\text{I.R. (neat, cm}^{-1}\text{)}$ 3065, 2929, 1659, 1605, 1524, 1493, 1347, 750, 694

$\text{HRMS } m/z$ $[(\text{M}+\text{H})^+]$ calcd for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_3\text{S}$ 456.1361 found 456.1382.

4-(5-(1-methyl-4-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)thiophen-2-yl)benzonitrile (84)



The title compound was prepared following the general protocol F using **72** (68 mg, 0.170 mmol), 4-cyanophenylboronic acid (27 mg, 0.184 mmol), $\text{Pd}(\text{PPh}_3)_4$ (16 mg, 0.014 mmol) and potassium carbonate (47 mg, 0.340 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 4/6) yielded the title compound (56 mg, 78%) as a yellow solid.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ (ppm) = 3.01 (s, 3H), 6.02 (s, 1H), 6.70 (d, $J = 8.1$ Hz, 1H), 6.87 (d, $J = 3.7$ Hz, 1H), 6.98 (t, $J = 7.5$ Hz, 1H), 7.16 (d, $J = 3.7$ Hz, 1H), 7.25-7.30 (m, 1H), 7.31-7.42 (m, 4H), 7.42-7.48 (m, 1H), 7.50-7.59 (m, 4H), 8.12 (dd, $J = 7.8$ Hz, $J' = 1.6$ Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ (ppm) = 36.5, 78.0, 111.0, 113.5, 117.9, 118.7, 119.7, 124.3, 126.1, 126.7, 127.3, 128.1, 129.3, 129.4, 132.7, 134.4, 138.0, 140.5, 141.8, 142.3, 146.2, 161.8

MS (ESI) $[M+H]^+ = 422.0$

LC/MS (XBridge 100 × 4.6 mm) : $t_R = 8.78\text{min}$, $m/z : 422.0$ ($[M+H]^+$)

Gradient A : $t_R = 22.39\text{ min}$

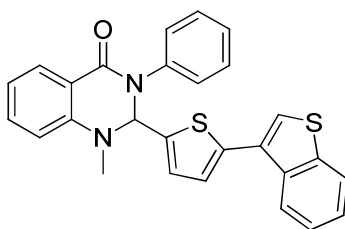
Gradient D : $t_R = 18.67\text{ min}$

I.R. (neat, cm^{-1}) 3064, 2956, 2887, 2225, 1659, 1604, 1494, 750, 694

HRMS m/z ($[M+H]^+$) calcd for $\text{C}_{26}\text{H}_{20}\text{N}_3\text{OS}$ 422.1333 found 422.1327.

2-(5-(benzo[b]thiophen-3-yl)thiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one

(85)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), thionaphthene-3-boronic acid (49 mg, 0.275 mmol), $\text{Pd}(\text{PPh}_3)_4$ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 4/6) yielded the title compound (67 mg, 59%) as a pale brown solid.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ (ppm) = 3.03 (s, 3H), 6.05 (s, 1H), 6.71 (d, $J = 8.1\text{ Hz}$, 1H), 6.92 (d, $J = 3.7\text{ Hz}$, 1H), 6.98(t, $J = 7.5\text{ Hz}$, 1H), 7.09 (d, $J = 3.7\text{ Hz}$, 1H), 7.29-7.48 (m, 9H), 7.84-7.88 (m, 1H), 7.98-8.02 (m, 1H), 8.15 (dd, $J = 7.8\text{ Hz}$, $J' = 1.6\text{ Hz}$, 1H)

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ (ppm) = 36.5, 78.1, 113.3, 117.8, 119.6, 122.9, 123.0, 124.1, 124.6, 124.8, 124.8, 126.8, 127.3, 127.4, 129.3, 129.9, 134.4, 136.9, 137.9, 139.0, 140.5, 140.6, 146.4, 162.0

MS (ESI) $[M+H]^+ = 452.9$

LC/MS (XBridge 100 × 4.6 mm) : $t_R = 9.32$ min, $m/z : 452.9$ ($[M+H]^+$)

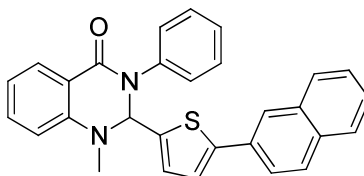
Gradient A : $t_R = 24.95$ min

Gradient D : $t_R = 22.35$ min

I.R. (neat, cm^{-1}) 3067, 2954, 2886, 1657, 1605, 1494, 750, 694

HRMS m/z $[(M+H)^+]$ calcd for $\text{C}_{27}\text{H}_{21}\text{N}_2\text{OS}_2$ 453.1107 found 453.1095.

1-methyl-2-(5-(naphthalen-2-yl)thiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (86)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), 2-naphthaleneboronic acid (47 mg, 0.273 mmol), $\text{Pd}(\text{PPh}_3)_4$ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 4/6) yielded the title compound (84 mg, 75%) as a yellow solid.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ (ppm) = 3.03 (s, 3H), 6.02 (s, 1H), 6.71 (d, $J = 8.1$ Hz, 1H), 6.88 (d, $J = 3.7$ Hz, 1H), 7.00 (t, $J = 7.5$ Hz, 1H), 7.18 (d, $J = 3.7$ Hz, 1H), 7.28-7.33 (m, 1H), 7.37-7.50 (m, 7H), 7.58-7.62 (m, 1H), 7.76-7.81 (m, 3H), 7.90-7.92 (m, 1H), 8.17 (dd, $J = 7.8$ Hz, $J' = 1.6$ Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ (ppm) = 36.4, 78.2, 113.3, 117.8, 119.6, 122.5, 124.1, 124.4, 126.3, 126.7, 126.8, 127.4, 127.8, 128.0, 128.1, 128.7, 129.4, 129.4, 131.1, 132.9, 133.6, 134.4, 139.3, 140.6, 144.9, 146.4, 162.1

MS (ESI) $[M+H]^+ = 446.9$

LC/MS (XBridge 100 × 4.6 mm) : $t_R = 9.68$ min, $m/z : 446.9$ ($[M+H]^+$)

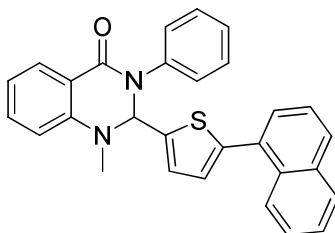
Gradient A : $t_R = 24.07$ min

Gradient D : $t_R = 22.32$ min

I.R. (neat, cm^{-1}) 3056, 2958, 1656, 1603, 1493, 748, 694

HRMS m/z $[(M+H)^+]$ calcd for $\text{C}_{29}\text{H}_{23}\text{N}_2\text{OS}$ 447.1532 found 447.1531.

1-methyl-2-(5-(naphthalen-1-yl)thiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (87)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), 1-naphthaleneboronic acid (47 mg, 0.273 mmol), $\text{Pd}(\text{PPh}_3)_4$ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 4/6) yielded the title compound (97 mg, 87%) as a pale brown solid.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ (ppm) = 3.05 (s, 3H), 6.09 (s, 1H), 6.73 (d, $J = 8.1$ Hz, 1H), 6.95 (d, $J = 3.7$ Hz, 1H), 6.98 (t, $J = 7.5$ Hz, 1H), 7.02 (d, $J = 3.7$ Hz, 1H), 7.31-7.36 (m, 1H), 7.43-7.52 (m, 9H), 7.81-7.90 (m, 2H), 8.11-8.17 (m, 2H)

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ (ppm) = 36.4, 78.2, 113.3, 117.7, 119.4, 125.2, 125.4, 126.1, 126.4, 126.6, 126.8, 127.2, 127.3, 128.2, 128.4, 128.7, 129.3, 131.5, 131.6, 133.8, 134.3, 139.9, 140.7, 142.3, 146.5, 162.1

MS (ESI) $[\text{M}+\text{H}]^+ = 446.9$

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 9.52$ min, m/z : 446.9 ($[\text{M}+\text{H}]^+$)

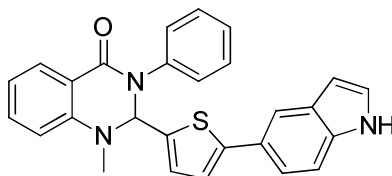
Gradient A : $t_R = 25.09$ min

Gradient D : $t_R = 22.17$ min

I.R. (neat, cm^{-1}) 3058, 2925, 1655, 1605, 1492, 749, 694

HRMS m/z $[(M+H)^+]$ calcd for $\text{C}_{29}\text{H}_{23}\text{N}_2\text{OS}$ 447.1532 found 447.1531.

2-(5-(1H-indol-5-yl)thiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (88)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), 5-indoleboronic acid pinacol ester (67 mg, 0.276 mmol), $\text{Pd}(\text{PPh}_3)_4$ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 5/5) yielded the title compound (69 mg, 63%) as a pale yellow solid.

$^1\text{H-NMR}$ (400MHz, DMSO-d_6) δ (ppm) = 2.99 (s, 3H), 5.76 (s, 1H), 6.40-6.44 (m, 1H), 6.47 (s, 1H), 6.80 (d, $J = 8.1$ Hz, 1H), 6.90-6.96 (m, 2H), 7.17 (d, $J = 3.7$ Hz, 1H), 7.20-7.50 (m, 9H), 7.66 (d, $J = 1.6$ Hz, 1H), 7.90 (dd, $J = 7.7$ Hz, $J' = 1.6$ Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO-d_6) δ (ppm) = 35.1, 75.9, 112.0, 113.2, 116.9, 118.6, 119.2, 120.7, 124.3, 126.4, 126.5, 126.7, 128.0, 128.2, 128.4, 128.8, 131.4, 131.5, 134.3, 135.6, 137.1, 140.2, 145.5, 146.5, 160.9

MS (ESI) $[(M+H)^+]$ = 436.2

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 8.13$ min, m/z : 436.2 ($[(M+H)^+]$)

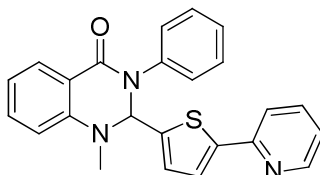
Gradient A : $t_R = 22.35$ min

Gradient D : $t_R = 18.35$ min

I.R. (neat, cm^{-1}) 3244, 3056, 2958, 1622, 1597, 1492, 737, 694

HRMS m/z [(M+H)⁺] calcd for $\text{C}_{27}\text{H}_{22}\text{N}_3\text{OS}$ 436.1476 found 436.1484.

1-methyl-3-phenyl-2-(5-(pyridin-2-yl)thiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (89)



The title compound was prepared following the general protocol E using NaH (13 mg, 0.325 mmol), **23** (100 mg, 0.261 mmol) and iodomethane (18 μL , 0.289 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (89 mg, 69%) as a white solid.

¹H-NMR (400MHz, CDCl_3) δ (ppm) = 2.91 (s, 3H), 5.90 (s, 1H), 6.55 (d, $J = 8.1\text{Hz}$, 1H), 6.77 (d, $J = 3.5\text{ Hz}$, 1H), 6.83 (t, $J = 7.5\text{ Hz}$, 1H), 7.00 (ddd, $J = 7.6\text{ Hz}$, $J' = 4.9\text{ Hz}$, $J'' = 1.1\text{ Hz}$, 1H), 7.12-7.17 (m, 1H), 7.20-7.33 (m, 6H), 7.41 (dt, $J = 8.1\text{ Hz}$, $J' = 1.1\text{ Hz}$, 1H), 7.51 (td, $J = 7.6\text{ Hz}$, $J' = 1.8\text{ Hz}$, 1H), 7.99 (dd, $J = 7.8\text{ Hz}$, $J' = 1.6\text{ Hz}$, 1H), 8.37 (ddd, $J = 4.9\text{ Hz}$, $J' = 1.6\text{ Hz}$, $J'' = 1.1\text{ Hz}$, 1H)

¹³C-NMR (100MHz, CDCl_3) δ (ppm) = 36.5, 77.9, 113.3, 117.8, 119.0, 119.5, 122.3, 123.9, 126.6, 127.2, 127.9, 129.3, 129.4, 134.3, 136.9, 140.7, 142.0, 145.0, 146.2, 149.5, 151.9, 162.0

MS (ESI) [M+H]⁺ = 398.1

LC/MS (XBridge 100 \times 4.6 mm) :

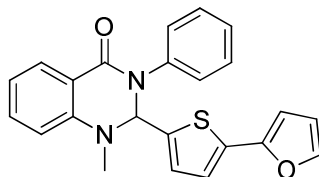
Gradient A : $t_R = 20.15\text{ min}$

Gradient D : $t_R = 17.25\text{ min}$

I.R. (neat, cm^{-1}) 3064, 2918, 2862, 1653, 1605, 1494, 750, 694

HRMS m/z [(M+H)⁺] calcd for C₂₄H₂₀N₃OS 398.1346 found 398.1327.

2-(5-(furan-2-yl)thiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (90)



The title compound was prepared following the general protocol E using NaH (14 mg, 0.325 mmol), **24** (100 mg, 0.268 mmol) and iodomethane (18 μ L, 0.289 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (100 mg, 97%) as a white solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 2.96 (s, 3H), 5.98 (s, 1H), 6.36-6.41 (m, 2H), 6.67 (d, J = 8.1 Hz, 1H), 6.77 (d, J = 3.7 Hz, 1H), 6.93-7.00 (m, 2H), 7.25-7.46 (m, 7H), 8.12 (dd, J = 7.7 Hz, J' = 1.6 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 36.3, 78.0, 105.8, 11.8, 113.3, 117.8, 119.5, 121.4, 126.8, 127.3, 127.5, 129.3, 129.3, 134.1, 134.4, 138.4, 140.6, 142.0, 146.3, 148.7, 161.9

MS (ESI) [M+H]⁺ = 387.1

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 8.72 min, m/z : 387.1 ([M+H]⁺)

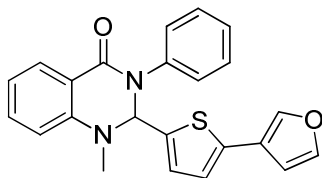
Gradient A : t_R = 21.92 min

Gradient D : t_R = 18.77 min

I.R. (neat, cm⁻¹) 3070, 2956, 2886, 1655, 1605, 1493, 749, 694

HRMS m/z [(M+H)⁺] calcd for C₂₃H₁₉N₂O₂S 387.1169 found 387.1167.

2-(5-(furan-3-yl)thiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (91)



The title compound was prepared following the general protocol F using **72** (100 mg, 0.250 mmol), 3-furanylboronic acid (31 mg, 0.277 mmol), Pd(PPh₃)₄ (23 mg, 0.020 mmol) and potassium carbonate (69 mg, 0.500 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 4/6) yielded the title compound (77 mg, 80%) as a pale yellow solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 2.97 (s, 3H), 5.97 (s, 1H), 6.48-6.50 (m, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 3.6 Hz, 1H), 6.83 (d, *J* = 3.6 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 7.25-7.31 (m, 1H), 7.31-7.40 (m, 5H), 7.42-7.47 (m, 1H), 7.55 (brs, 1H), 8.12 (dd, *J* = 7.8 Hz, *J*' = 1.5 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 36.2, 78.0, 109.1, 113.2, 117.6, 119.4, 120.1, 122.3, 126.8, 127.3, 127.4, 129.2, 134.3, 135.4, 137.8, 138.5, 140.5, 143.7, 146.3, 161.9

MS (ESI) [M+H]⁺ = 387.1

LC/MS (XBridge 100 × 4.6 mm) : t_R = 8.27 min, m/z : 387.1 ([M+H⁺])

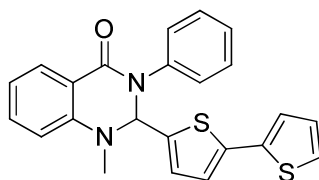
Gradient A : t_R = 21.85 min

Gradient D : t_R = 18.60 min

I.R. (neat, cm⁻¹) 3070, 2955, 2887, 1657, 1605, 1494, 871, 750, 695

HRMS m/z [(M+H)⁺] calcd for C₂₃H₁₉N₂O₂S 387.1155 found 387.1167.

2-([2,2'-bithiophen]-5-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (92)



The title compound was prepared following the general protocol E using NaH (13 mg, 0.325 mmol), **22** (100 mg, 0.257 mmol) and iodomethane (18 μ L, 0.289 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 3/7) yielded the title compound (98 mg, 95%) as a white solid.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ (ppm) = 2.98 (s, 3H), 5.96 (s, 1H), 6.68 (d, $J = 8.1$ Hz, 1H), 6.76 (d, $J = 3.7$ Hz, 1H), 6.90 (d, $J = 3.7$ Hz, 1H), 6.93-7.00 (m, 2H), 7.05 (dd, $J = 3.7$ Hz, $J' = 1.2$ Hz, 1H), 7.17 (dd, $J = 5.1$ Hz, $J' = 1.2$ Hz, 1H), 7.26-7.48 (m, 6H), 8.12 (dd, $J = 7.7$ Hz, $J' = 1.6$ Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, CDCl_3) δ (ppm) = 36.4, 78.1, 113.3, 117.8, 119.6, 122.6, 124.3, 124.9, 126.8, 127.3, 127.6, 127.9, 129.3, 134.4, 136.7, 137.9, 138.6, 140.6, 146.3, 161.9

MS (ESI) $[\text{M}+\text{H}]^+$ = 403.1

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 9.20$ min, m/z : 403.1 ($[\text{M}+\text{H}]^+$)

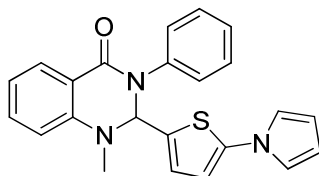
Gradient A : $t_R = 22.67$ min

Gradient D : $t_R = 19.77$ min

I.R. (neat, cm^{-1}) 3069, 2963, 2885, 1655, 1604, 1493, 750, 694

HRMS m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{19}\text{N}_2\text{OS}_2$ 403.0942 found 403.0939.

2-(5-(1H-pyrrol-1-yl)thiophen-2-yl)-1-methyl-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (93)



A mixture of **72** (100 mg, 0.250 mmol), pyrrole (21 μ L, 0.298 mmol), *trans*-*N,N'*-Dimethyl-1,2-cyclohexanediamine (16 μ L, 0.100 mmol), Copper (I) iodide (14 mg, 0.074 mmol) and cesium carbonate (163 mg, 0.500 mmol) in degassed anhydrous DMF (2.5mL, 0.1M) was stirred at 110 °C in a sealed tube for 24h. The reaction mixture was cooled to room temperature and EtOAc was added. The mixture was then filtered through a silica pad, washed with EtOAc. The filtrate was then concentrated under reduced pressure. The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 3/7) yielded the title compound (58 mg, 60%) as a beige solid.

¹H-NMR (400MHz, DMSO-*d*₆) δ (ppm) = 2.98 (s, 3H), 6.18 (t, *J* = 2.2 Hz, 2H), 6.45 (s, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 3.8 Hz, 1H), 6.91 (t, *J* = 3.8 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 7.06 (t, *J* = 2.2 Hz, 2H), 7.27-7.51 (m, 6H), 7.88 (dd, *J* = 7.8 Hz, *J'* = 1.6 Hz, 1H)

¹³C-NMR (100MHz, DMSO-*d*₆) δ (ppm) = 35.1, 75.9, 110.8, 113.4, 113.6, 116.8, 118.8, 120.6, 126.6, 126.8, 128.3, 128.9, 132.3, 134.4, 140.0, 142.6, 146.4, 160.7

MS (ESI) [M+H]⁺ = 385.9

LC/MS (XBridge 100 \times 4.6 mm) : *t_R* = 8.83 min, *m/z* : 385.9 ([M+H⁺])

Gradient A : *t_R* = 22.92 min

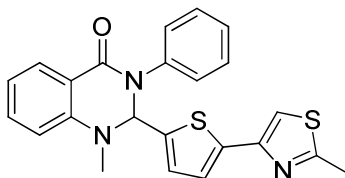
Gradient D : *t_R* = 19.04 min

I.R. (neat, cm⁻¹) 3072, 2925, 2885, 1656, 1606, 1592, 1499, 1321, 750, 726, 694

HRMS *m/z* [(M+H)^{+ calcd for C₂₃H₂₀N₃OS 386.1344 found 386.1344.}

1-methyl-2-(5-(2-methylthiazol-4-yl)thiophen-2-yl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one

(94)



The title compound was prepared following the general protocol E using NaH (19 mg, 0.475 mmol), **25** (100 mg, 0.248 mmol) and iodomethane (17 μ L, 0.273 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/heptane 2/8) yielded the title compound (86 mg, 83%) as a white solid.

¹H-NMR (400MHz, CDCl₃) δ (ppm) = 2.70 (s, 3H), 2.99 (s, 3H), 5.98 (s, 1H), 6.66 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 3.8 Hz, 1H), 6.92-6.99 (m, 1H), 7.09 (s, 1H), 7.17 (d, J = 3.8 Hz, 1H), 7.24-7.39 (m, 5H), 7.40-7.46 (m, 1H), 8.10 (dd, J = 7.8 Hz, J' = 1.6 Hz, 1H)

¹³C-NMR (100MHz, CDCl₃) δ (ppm) = 19.3, 36.4, 78.1, 111.9, 113.3, 117.8, 119.5, 123.2, 126.8, 127.3, 127.6, 129.3, 129.4, 134.3, 138.6, 139.4, 140.6, 146.3, 148.8, 162.0, 166.5

MS (ESI) [M+H]⁺ = 417.8

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 8.68 min, m/z : 417.8 ([M+H⁺])

Gradient A : t_R = 20.92 min

Gradient D : t_R = 17.87 min

I.R. (neat, cm⁻¹) 3075, 2958, 2871, 1651, 1605, 1494, 749, 696

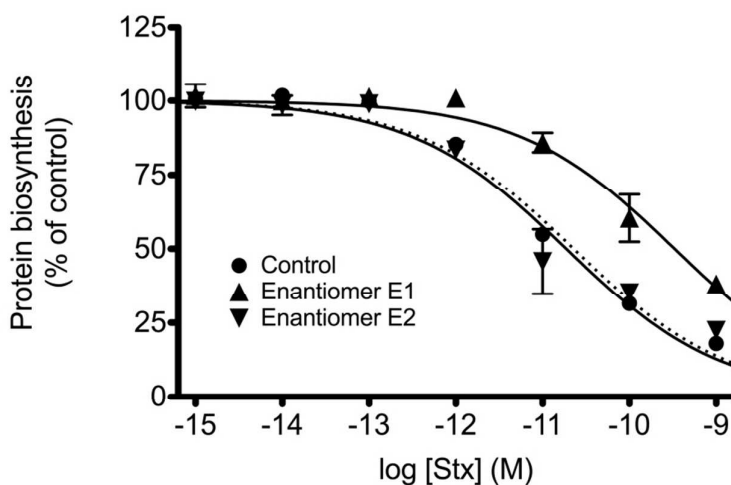
HRMS m/z [(M+H)⁺] calcd for C₂₃H₂₀N₃OS₂ 418.1048 found 418.1048.

HPLC Chiral Chirapak IB : EtOH/Hexane 40/60

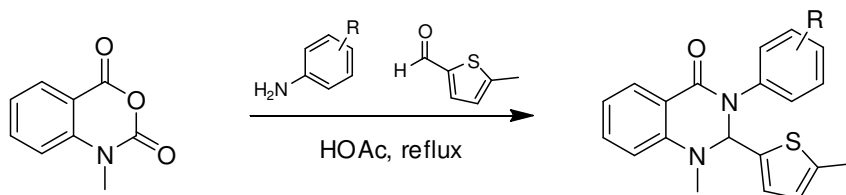
Enantiomer 1: t_R = 10.69 min

Enantiomer 2: $t_R = 17.78$ min

Evaluation of the activity towards Stx cytotoxicity of each enantiomer of **94** (30 μ M). HeLa cells were incubated for 4 hours with Enantiomer 1 (\blacktriangle), Enantiomer 2 (\blacktriangledown) or carrier only (DMSO, black-filled circles) before the addition of Stx at the indicated concentrations for 20 hr. Media was removed and replaced with DMEM containing [14 C]-leucine at 0.5 μ Ci/mL for 7 hr before counting. Each data point represents the mean of duplicate \pm SD of a representative experiment.

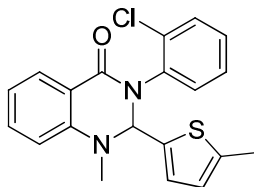


GENERAL PROCEDURE G: multicomponent



A mixture of N-methylisatoic anhydride (1 equiv), aniline derivative (1 equiv) and 5-methylthiophen-2-carboxaldehyde (1 equiv) in acetic acid (0.5M) was refluxed until complete consumption of starting materials. Acetic acid was removed under reduced pressure and the residue was diluted in EtOAc. The organic layer was washed with a saturated solution of NaHCO₃ (2 x 20mL) and brine (2 x 20mL), dried over anhydrous Na₂SO₄, filtered and concentrate in vacuo. The purification of the crude mixture by silica gel chromatography yielded the title compound.

3-(2-chlorophenyl)-1-methyl-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (95)



The title compound was prepared following the general protocol G using N-methylmisatoic anhydride (354 mg, 2.00 mmol), 2-chloroaniline (210 μ L, 2.00 mmol) and 5-methylthiophen-2-carboxaldehyde (218 μ L, 2.00 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 3/7) yielded the title compound (496 mg, 67%) as a white solid.

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ (ppm) = 2.31 (s, 3H), 2.87 (s, 3H), 6.07 (s, 1H), 6.57-6.61 (m, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 3.4 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.95 (dd, J = 7.9 Hz, J' = 1.6 Hz, 1H), 7.31 (td, J = 7.7 Hz, J' = 1.4 Hz, 1H), 7.40 (td, J = 7.9 Hz, J' = 1.6 Hz, 1H), 7.48 (td, J = 7.6 Hz, J' = 1.6 Hz, 1H), 7.66 (dd, J = 8.0 Hz, J' = 1.6 Hz, 1H), 7.82 (dd, J = 7.7 Hz, J' = 1.6 Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ (ppm) = 14.9, 34.8, 75.4, 113.1, 116.1, 118.3, 124.4, 127.7, 128.1, 129.6, 130.1, 130.9, 131.4, 134.5, 136.6, 137.0, 139.8, 146.8, 160.6

MS (ESI) $[\text{M}+\text{H}]^+$ = 370.7

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 8.67 min, m/z : 370.7 ($[\text{M}+\text{H}]^+$)

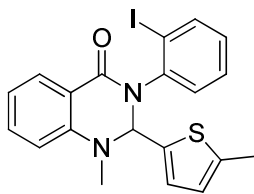
Gradient A : t_R = 22.55 min

Gradient D : t_R = 18.80 min

I.R. (neat, cm^{-1}) 3069, 2918, 2885, 1660, 1606, 1493, 750, 692

HRMS m/z $[(\text{M}+\text{H})^+]$ calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{OS}^{35}\text{Cl}$ 369.0835 found 369.0828.

3-(2-iodophenyl)-1-methyl-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (96)



The title compound was prepared following the general protocol G using N-methylisatoic anhydride (354 mg, 2.00 mmol), 2-iodoaniline (438 mg, 2.00 mmol) and 5-methylthiophen-2-carboxaldehyde (218 μ L, 2.00 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 2/8) yielded the title compound (428 mg, 46%) as a white solid.

¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 2.31 (s, 3H), 2.87 (s, 3H), 5.97 (s, 1H), 6.58-6.60 (m, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 3.6 Hz, 1H), 6.82 (dd, J = 8.0 Hz and J' = 1.2 Hz, 1H), 6.90 (t, J = 7.6 Hz, 1H), 7.13 (td, J = 7.6 Hz and J' = 1.2 Hz, 1H), 7.33-7.38 (m, 1H), 7.46-7.50 (m, 1H), 7.82 (dd, J = 7.6 Hz and J' = 1.2 Hz, 1H), 8.02 (dd, J = 8.0 Hz and J' = 1.2 Hz, 1H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 14.9, 34.7, 75.9, 100.2, 112.9, 116.1, 118.1, 124.3, 126.5, 128.1, 128.2, 128.8, 128.9, 129.9, 130.3, 134.5, 136.4, 139.5, 139.7, 142.1, 146.7, 160.4

MS (ESI) [M+H]⁺ = 460.9

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 8.95 min, m/z : 460.9 ([M+H]⁺)

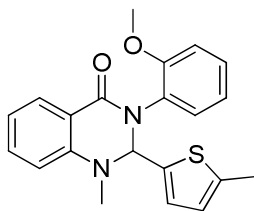
Gradient A : t_R = 22.95 min

Gradient D : t_R = 19.04 min

I.R. (neat, cm⁻¹) 3065, 2918, 2884, 1660, 1607, 1493, 748, 693

HRMS m/z [(M+H)⁺] calcd for C₂₀H₁₈N₂O₂S 461.0204 found 461.0185.

3-(2-methoxyphenyl)-1-methyl-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (97)



The title compound was prepared following the general protocol G using N-methylmisatoic anhydride (354 mg, 2.00 mmol), *o*-anisidine (225 μ L, 2.00 mmol) and 5-methylthiophen-2-carboxaldehyde (218 μ L, 2.00 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 4/6) yielded the title compound (207 mg, 28%) as a beige solid.

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ (ppm) = 2.29 (s, 3H), 2.85 (s, 3H), 3.78 (s, 3H), 6.00 (s, 1H), 6.52-6.57 (m, 1H), 6.71 (d, J = 3.4 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.84-6.93 (m, 2H), 6.94-7.00 (m, 1H), 7.14 (d, J = 3.1 Hz, 1H), 7.31 (td, J = 8.5 Hz, J' = 1.7 Hz, 1H), 7.45 (td, J = 8.5 Hz, J' = 1.7 Hz, 1H), 7.81 (dd, J = 7.7 Hz, J' = 1.7, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ (ppm) = 14.8, 35.0, 55.7, 75.4, 112.5, 113.0, 116.8, 118.1, 120.1, 124.2, 127.4, 128.0, 128.0, 128.9, 130.0, 134.1, 137.5, 139.3, 146.6, 154.5, 160.4

MS (ESI) $[\text{M}+\text{H}]^+ = 366.1$

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 8.28$ min, m/z : 366.1 ($[\text{M}+\text{H}]^+$)

Gradient A : $t_R = 22.12$ min

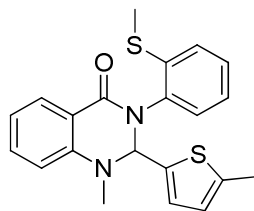
Gradient D : $t_R = 17.39$ min

I.R. (neat, cm^{-1}) 3069, 2919, 2885, 1660, 1606, 1504, 1493, 749, 694

HRMS m/z $[(\text{M}+\text{H})^+]$ calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$ 365.1325 found 365.1324.

1-methyl-3-(2-(methylthio)phenyl)-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one

(98)



The title compound was prepared following the general protocol G using N-methylmisatoic anhydride (354 mg, 2.00 mmol), 2-(methylmercapto)aniline (251 μ L, 2.00 mmol) and 5-methylthiophen-2-carboxaldehyde (218 μ L, 2.00 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/ cyclohexane 3/7) yielded the title compound (557 mg, 73%) as a beige solid.

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ (ppm) = 2.31 (s, 3H), 2.40 (s, 3H), 2.85 (s, 3H), 5.92 (s, 1H), 6.56-6.59 (m, 1H), 6.72-6.79 (m, 3H), 6.89 (d, $J = 7.3$ Hz, 1H), 7.06-7.12 (m, 1H), 7.33-7.40 (m, 2H), 7.47 (d, $J = 7.8$ Hz, 1H), 7.82 (dd, $J = 7.8$ Hz, $J' = 1.7$ Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ (ppm) = 13.6, 14.9, 34.8, 75.2, 112.9, 116.3, 118.1, 124.3, 124.5, 125.1, 128.1, 128.7, 129.7, 134.4, 136.0, 136.6, 137.4, 139.6, 146.7, 160.6

MS (ESI) $[\text{M}+\text{H}]^+$ = 381.0

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 8.78$ min, m/z : 381.0 ($[\text{M}+\text{H}]^+$)

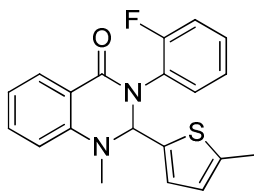
Gradient A : $t_R = 22.84$ min

Gradient D : $t_R = 18.57$ min

I.R. (neat, cm^{-1}) 3060, 2920, 2884, 1659, 1606, 1493, 749, 692

HRMS m/z $[(\text{M}+\text{H})^+]$ calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{OS}_2$ 381.1079 found 381.1095.

3-(2-fluorophenyl)-1-methyl-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (99)



The title compound was prepared following the general protocol G using N-methylisatoic anhydride (354 mg, 2.00 mmol), 2-fluoroaniline (193 μ L, 2.00 mmol) and 5-methylthiophen-2-carboxaldehyde (218 μ L, 2.00 mmol). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 2/8) yielded the title compound (361 mg, 51%) as a pale yellow solid.

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ (ppm) = 2.30 (s, 3H), 2.87 (s, 3H), 6.24 (s, 1H), 6.55-6.59 (m, 1H), 6.74-6.79 (m, 2H), 6.92 (t, $J = 7.4$ Hz, 1H), 7.19-7.27 (m, 2H), 7.28-7.35 (m, 1H), 7.36-7.44 (m, 1H), 7.45-7.52 (m, 1H), 7.83 (dd, $J = 7.7$ Hz, $J' = 1.6$ Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO- d_6) δ (ppm) = 14.8, 34.9, 75.8, 113.2, 116.3, 116.5, 118.5, 124.3, 124.7, 124.8, 127.4, 127.5, 127.6, 128.1, 129.5, 129.5, 134.5, 136.8, 139.7, 146.8, 156.2, 158.6, 160.4

MS (ESI) $[\text{M}+\text{H}]^+ = 353.9$

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 8.37$ min, m/z : 353.9 ($[\text{M}+\text{H}]^+$)

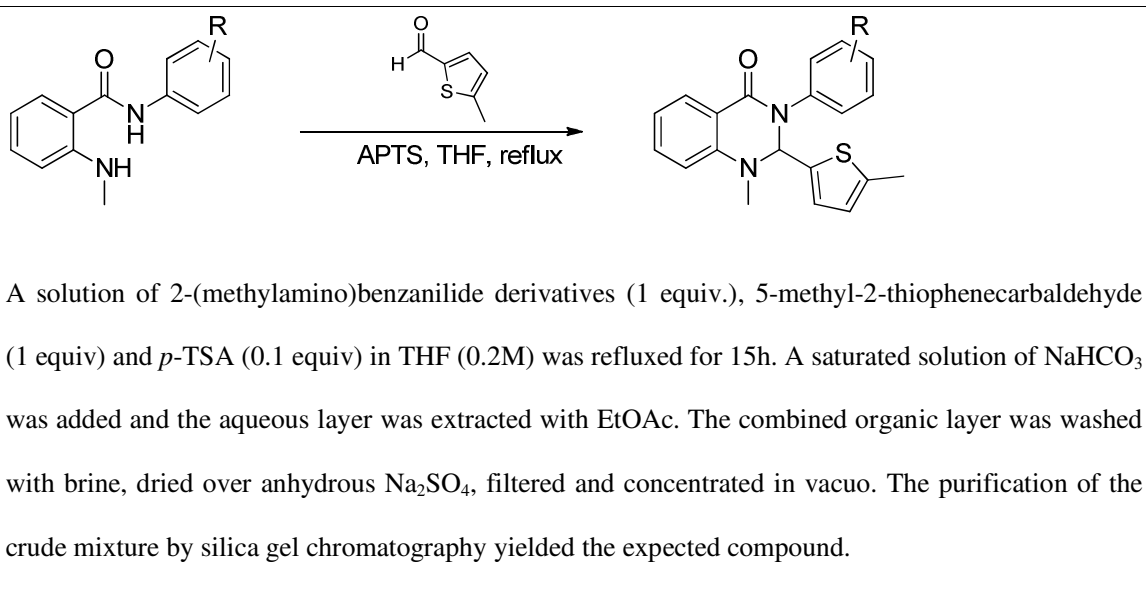
Gradient A : $t_R = 21.99$ min

Gradient D : $t_R = 17.80$ min

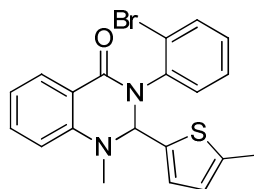
I.R. (neat, cm^{-1}) 3071, 2919, 2885, 1660, 1607, 1500, 750

HRMS m/z $[(\text{M}+\text{H})^+]$ calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{OSF}$ 353.1137 found 353.1124.

GENERAL PROCEDURE H:



3-(2-bromophenyl)-1-methyl-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (100)



The title compound was prepared following the general protocol H using N-(2-bromophenyl)-2-(methylamino)benzamide (100 mg, 0.328 mmol), 5-methyl-2-thiophenecarbaldehyde (36 μ L, 0.330 mmol) and *p*-TSA (6 mg, 0.035). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 2/8) yielded the title compound (86 mg, 63%) as a white solid.

¹H-NMR (400MHz, DMSO-d₆) δ (ppm) = 2.31 (s, 3H), 2.87 (s, 3H), 6.04 (s, 1H), 6.57-6.60 (m, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 3.4 Hz, 1H), 6.88-6.94 (m, 2H), 7.28-7.39 (m, 2H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.82 (td, *J* = 9.6 Hz, *J'* = 1.9 Hz, 2H)

¹³C-NMR (100MHz, DMSO-d₆) δ (ppm) = 14.9, 34.8, 75.5, 113.0, 116.1, 118.2, 122.3, 124.3, 128.1, 128.1, 128.2, 129.9, 131.2, 133.3, 134.5, 136.5, 138.5, 139.8, 146.7, 160.5

MS (ESI) [M+H]⁺ = 412.9, 415.1

LC/MS (XBridge 100 × 4.6 mm) : $t_R = 8.33$ min, m/z : 412.9, 415.1 ($[M+H]^+$)

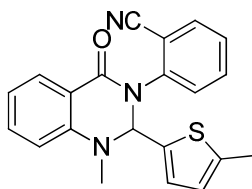
Gradient A : $t_R = 23.12$ min

Gradient D : $t_R = 20.00$ min

I.R. (neat, cm^{-1}) 3068, 2918, 2885, 1661, 1606, 1493, 1475, 749

HRMS m/z $[(M+H)^+]$ calcd for $C_{20}H_{18}N_2OS^{79}Br$ 413.0314 found 413.0323.

2-(1-methyl-2-(5-methylthiophen-2-yl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)benzonitrile (101)



The title compound was prepared following the general protocol H using N-(2-cyanophenyl)-2-(methylamino)benzamide (100 mg, 0.398 mmol), 5-methyl-2-thiophenecarbaldehyde (44 μ L, 0.403 mmol) and *p*-TSA (7 mg, 0.041). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 4/6) yielded the title compound (69 mg, 48%) as a white solid.

1H -NMR (400MHz, DMSO- d_6) δ (ppm) = 2.31 (s, 3H), 2.90 (s, 3H), 6.38 (s, 1H), 6.60 (s, 1H), 6.74-6.86 (m, 2H), 6.94 (t, $J = 7.5$ Hz, 1H), 7.22 (brs, 1H), 7.47-7.60 (m, 2H), 7.74 (t, $J = 7.8$ Hz, 1H), 7.85 (dd, $J = 7.7$ Hz, $J' = 1.5$ Hz, 1H), 7.95 (d, $J = 7.6$ Hz, 1H)

^{13}C -NMR (100MHz, DMSO- d_6) δ (ppm) = 14.8, 34.9, 75.9, 113.3, 116.0, 116.4, 118.5, 124.4, 128.0, 128.3, 128.7, 133.6, 134.1, 134.8, 136.4, 140.0, 142.2, 146.9

MS (ESI) $[M+H]^+$ = 360.3

LC/MS (XBridge 100 × 4.6 mm) : $t_R = 7.58$ min, m/z : 360.3 ($[M+H]^+$)

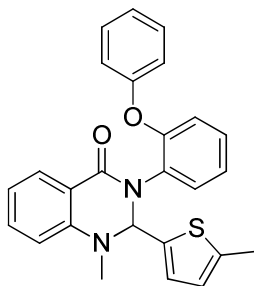
Gradient B: $t_R = 21.09$ min

Gradient E : $t_R = 17.89$ min

I.R. (neat, cm^{-1}) 3071, 2919, 2885, 2230, 1663, 1607, 1492, 755

HRMS m/z $[(M+H)^+]$ calcd for $\text{C}_{21}\text{H}_{18}\text{N}_3\text{OS}$ 360.1174 found 360.1171.

1-methyl-2-(5-methylthiophen-2-yl)-3-(2-phenoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (102)



The title compound was prepared following the general protocol H using 2-(methylamino)-N-(2-phenoxyphenyl)benzamide (127 mg, 0.399 mmol), 5-methyl-2-thiophenecarbaldehyde (44 μL , 0.403 mmol) and *p*-TSA (7 mg, 0.041). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 2/8) yielded the title compound (111 mg, 65%) as a white solid.

$^1\text{H-NMR}$ (400MHz, DMSO-d_6) δ (ppm) = 2.27 (s, 3H), 2.77 (s, 3H), 6.12 (s, 1H), 6.54-6.58 (m, 1H), 6.66 (d, $J = 8.1$ Hz, 1H), 6.78 (d, $J = 3.5$ Hz, 1H), 6.82-6.88 (m, 1H), 6.96 (m, 3H), 7.06-7.11 (m, 1H), 7.11-7.19 (m, 2H), 7.29-7.37 (m, 3H), 7.39-7.44 (m, 1H), 7.77 (dd, $J = 7.8$ Hz, $J' = 1.6$ Hz, 1H)

$^{13}\text{C-NMR}$ (100MHz, DMSO-d_6) δ (ppm) = 14.8, 34.9, 75.8, 112.9, 116.4, 118.2, 118.3, 123.4, 123.7, 124.2, 127.5, 128.0, 129.2, 129.8, 130.5, 130.9, 134.2, 137.1, 139.6, 146.5, 156.5, 160.4

MS (ESI) $[M+H]^+ = 427.1$

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 8.85$ min, m/z : 427.1 ($[M+H]^+$)

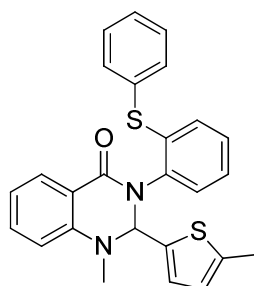
Gradient A : $t_R = 24.72$ min

Gradient D : $t_R = 20.14$ min

I.R. (neat, cm^{-1}) 3065, 2918, 2885, 1659, 1490, 1218, 750, 692

HRMS m/z [(M+H)⁺] calcd for $\text{C}_{26}\text{H}_{23}\text{N}_2\text{O}_2\text{S}$ 427.1467 found 427.1480.

1-methyl-2-(5-methylthiophen-2-yl)-3-(2-(phenylthio)phenyl)-2,3-dihydroquinazolin-4(1H)-one
(103)



The title compound was prepared following the general protocol H using 2-(methylamino)-N-(2-(phenylthio)phenyl)benzamide (134 mg, 0.401 mmol), 5-methyl-2-thiophenecarbaldehyde (44 μL , 0.403 mmol) and *p*-TSA (7 mg, 0.041). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 2/8) yielded the title compound (56 mg, 32%) as a white solid.

¹H-NMR (400MHz, DMSO- d_6) δ (ppm) = 2.32 (s, 3H), 2.83 (s, 3H), 6.05 (s, 1H), 6.59-6.61 (m, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 3.6 Hz, 1H), 6.86-6.91 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 6.8 Hz, 1H), 7.29 (t, *J* = 6.8 Hz, 1h), 7.37-7.49 (m, 6H), 7.81 (d, *J* = 7.6 Hz, 1H)

¹³C-NMR (100MHz, DMSO- d_6) δ (ppm) = 14.9, 34.9, 75.7, 112.9, 116.2, 118.1, 124.3, 127.1, 128.0, 128.1, 128.3, 128.9, 129.7, 130.0, 130.3, 132.7, 134.4, 135.4, 136.7, 138.1, 139.7, 146.6, 160.8

MS (ESI) [(M+H)⁺] = 443.0

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 9.22 min, m/z : 443.0 [(M+H⁺)]

Gradient A : t_R = 25.82 min

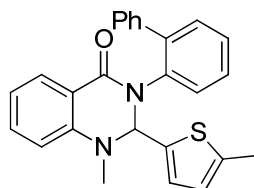
Gradient D : t_R = 21.02 min

I.R. (neat, cm^{-1}) 3068, 2920, 2884, 1653, 1604, 1494, 749, 694

HRMS m/z [(M+H)⁺] calcd for $\text{C}_{26}\text{H}_{23}\text{N}_2\text{OS}_2$ 443.1252 found 443.1252.

3-([1,1'-biphenyl]-2-yl)-1-methyl-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one

(104)



The title compound was prepared following the general protocol H using N-([1,1'-biphenyl]-2-yl)-2-(methylamino)benzamide (121 mg, 0.400 mmol), 5-methyl-2-thiophenecarbaldehyde (44 μL , 0.403 mmol) and *p*-TSA (7 mg, 0.041). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 2/8) yielded the title compound (122 mg, 74%) as a white solid.

¹H-NMR (400MHz, DMSO- d_6) δ (ppm) = 2.28 (s, 3H), 2.45 (s, 3H), 5.62 (s, 1H), 6.55 (s, 1H), 6.58 (d, $J = 8.2$ Hz, 1H), 6.67 (s, 1H), 6.83 (t, $J = 7.3$ Hz, 1H), 7.20-7.59 (m, 9H), 7.75 (d, $J = 7.7$ Hz, 1H)

¹³C-NMR (100MHz, DMSO- d_6) δ (ppm) = 14.8, 34.6, 75.8, 112.8, 116.4, 117.9, 124.3, 127.4, 127.5, 127.9, 128.0, 128.2, 128.5, 129.9, 130.8, 134.1, 136.8, 137.4, 137.5, 138.3, 139.2, 139.5, 146.1, 161.2

MS (ESI) [M+H]⁺ = 411.0

LC/MS (XBridge 100 \times 4.6 mm) : $t_R = 8.88$ min, m/z : 411.0 ([M+H⁺])

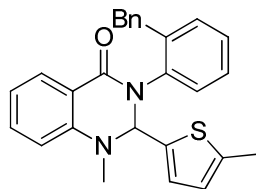
Gradient A : $t_R = 24.64$ min

Gradient D : $t_R = 20.24$ min

I.R. (neat, cm^{-1}) 3060, 2918, 2885, 1656, 1604, 1494, 1479, 750, 701

HRMS m/z [(M+H)⁺] calcd for $\text{C}_{26}\text{H}_{23}\text{N}_2\text{OS}$ 411.1529 found 411.1531.

3-(2-benzylphenyl)-1-methyl-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (105)



The title compound was prepared following the general protocol H using N-(2-benzylphenyl)-2-(methylamino)benzamide (127 mg, 0.401 mmol), 5-methyl-2-thiophenecarbaldehyde (44 μ L, 0.403 mmol) and *p*-TSA (7 mg, 0.041). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 2/8) yielded the title compound (134 mg, 79%) as a white solid.

¹H-NMR (400MHz, DMSO-*d*₆) δ (ppm) = 2.31 (s, 3H), 2.69 (s, 3H), 3.99 (q, *J* = 9.6 Hz, 2H), 5.78 (s, 1H), 6.58-6.60 (m, 1H), 6.70-6.73 (m, 2H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.91 (t, *J* = 7.2 Hz, 1H), 7.16-7.30 (m, 8H), 7.44-7.48 (m, 1H), 7.84 (dd, *J* = 8.0 Hz and *J*' = 1.6 Hz, 1H)

¹³C-NMR (100MHz, DMSO-*d*₆) δ (ppm) = 14.8, 34.6, 36.7, 76.0, 113.0, 116.7, 118.3, 124.3, 126.1, 126.8, 127.9, 128.1, 128.2, 128.4, 128.8, 129.0, 130.8, 134.3, 136.6, 138.6, 138.7, 139.7, 140.0, 146.6, 161.0

MS (ESI) [M+H]⁺ = 425.1

LC/MS (XBridge 100 \times 4.6 mm) : *t*_R = 9.28 min, *m/z* : 425.1 ([M+H]⁺)

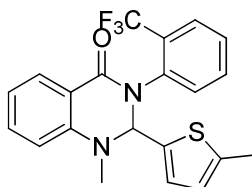
Gradient A : *t*_R = 25.60 min

Gradient D : *t*_R = 21.20 min

I.R. (neat, cm⁻¹) 3061, 2917, 1656, 1605, 1492, 1479, 750, 737, 696

HRMS *m/z* [(M+H)⁺] calcd for C₂₇H₂₅N₂OS 425.1671 found 425.1688.

1-methyl-2-(5-methylthiophen-2-yl)-3-(2-(trifluoromethyl)phenyl)-2,3-dihydroquinazolin-4(1H)-one (106)



The title compound was prepared following the general protocol H using 2-(methylamino)-N-(2-(trifluoromethyl)phenyl)benzamide (118 mg, 0.401 mmol), 5-methyl-2-thiophenecarbaldehyde (44 μ L, 0.403 mmol) and *p*-TSA (7 mg, 0.041). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 2/8) yielded the title compound (112 mg, 69%) as a white solid.

¹H-NMR (400MHz, DMSO-*d*₆) δ (ppm) = 2.33 (s, 3H), 2.82 (s, 3H), 6.00 (s, 1H), 6.60-6.62 (m, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.82-6.85 (m, 2H), 6.91 (t, *J* = 7.6 Hz, 1H), 7.47-7.51 (m, 1H), 7.60-7.68 (m, 2H), 7.81 (dd, *J* = 8.0 Hz and *J'* = 1.6 Hz, 1H), 7.90 (m, 1H)

¹³C-NMR (100MHz, DMSO-*d*₆) δ (ppm) = 14.9, 34.8, 76.4, 113.1, 115.7, 118.2, 122.0, 124.2, 124.7, 127.0, 127.1, 127.2, 127.2, 127.5, 127.7, 128.0, 128.9, 129.1, 131.8, 133.3, 134.6, 136.1, 137.7, 140.0, 146.8, 161.5

MS (ESI) [M+H]⁺ = 403.2

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 8.30 min, *m/z* : 403.2 ([M+H]⁺)

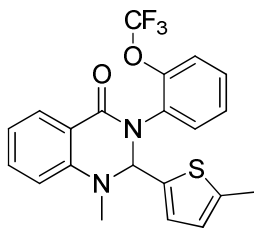
Gradient A : t_R = 23.55 min

Gradient D : t_R = 18.87 min

I.R. (neat, cm^{-1}) 3072, 2984, 2887, 1668, 1603, 1496, 803, 737

HRMS *m/z* [(M+H)^{+ calcd for C₂₁H₁₈N₂OSF₃ 403.1090 found 403.1092.}

1-methyl-2-(5-methylthiophen-2-yl)-3-(2-(trifluoromethoxy)phenyl)-2,3-dihydroquinazolin-4(1H)-one (107)



The title compound was prepared following the general protocol H using 2-(methylamino)-N-(2-(trifluoromethoxy)phenyl)benzamide (124 mg, 0.400 mmol), 5-methyl-2-thiophenecarbaldehyde (44 μ L, 0.403 mmol) and *p*-TSA (7 mg, 0.041). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 2/8) yielded the title compound (114 mg, 68%) as a white solid.

¹H-NMR (400MHz, DMSO-*d*₆) δ (ppm) = 2.30 (s, 3H), 2.88 (s, 3H), 6.14 (br s, 1H), 6.58 (br s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.81 (br s, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 7.12 (br s, 1H), 7.38-7.42 (m, 1H), 7.46-7.51 (m, 3H), 7.82 (dd, *J* = 7.6 Hz and *J'* = 1.2 Hz, 1H)

¹³C-NMR (100MHz, DMSO-*d*₆) δ (ppm) = 15.2, 35.3, 76.2, 113.6, 116.6, 118.8, 119.1, 121.6, 124.6, 124.7, 124.8, 128.2, 128.3, 128.5, 129.9, 130.9, 134.9, 137.2, 140.2, 147.2, 161.1

MS (ESI) [M+H]⁺ = 419.4

LC/MS (XBridge 100 \times 4.6 mm) : *t_R* = 8.55 min, *m/z* : 419.4 ([M+H⁺])

Gradient A : *t_R* = 23.92 min

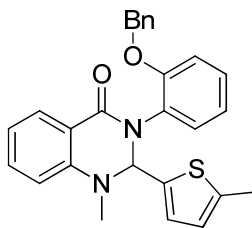
Gradient D : *t_R* = 19.42 min

I.R. (neat, cm⁻¹) 3075, 2961, 2886, 1664, 1604, 1497, 1256, 1218, 1168, 760, 694

HRMS *m/z* [(M+H)^{+ calcd for C₂₁H₁₈N₂O₂SF₃ 419.1032 found 419.1041.}

3-(2-(benzyloxy)phenyl)-1-methyl-2-(5-methylthiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one

(108)



The title compound was prepared following the general protocol H using N-(2-(benzyloxy)phenyl)-2-(methylamino)benzamide (133 mg, 0.400 mmol), 5-methyl-2-thiophenecarbaldehyde (52 μ L, 0.476 mmol) and *p*-TSA (7 mg, 0.041). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 2/8) yielded the title compound (127 mg, 72%) as a white solid.

¹H-NMR (400MHz, DMSO-*d*₆) δ (ppm) = 2.27 (s, 3H), 2.80 (s, 3H), 5.11-5.22 (m, 2H), 6.09 (s, 1H), 6.54 (br s, 1H), 6.71 (br s, 2H), 6.87-6.96 (m, 2H), 7.06 (br s, 1H), 7.23-7.52 (m, 8H), 7.82 (d, *J* = 6.4 Hz, 1H)

¹³C-NMR (100MHz, DMSO-*d*₆) δ (ppm) = 14.8, 34.9, 69.5, 75.4, 112.8, 113.8, 116.8, 118.1, 120.4, 124.2, 127.2, 127.3, 127.6, 128.0, 128.2, 128.8, 130.2, 134.1, 137.0, 137.2, 139.3, 146.6, 153.4, 160.5

MS (ESI) [M+H]⁺ = 441.2

LC/MS (XBridge 100 \times 4.6 mm) : t_R = 8.88min, *m/z* : 441.2 ([M+H⁺])

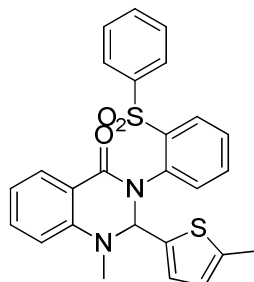
Gradient A : t_R = 25.42 min

Gradient D : t_R = 21.02 min

I.R. (neat, *cm*⁻¹) 3063, 2918, 2885, 1661, 1651, 1599, 1495, 1263, 747, 695

HRMS *m/z* [(M+H)^{+ calcd for C₂₇H₂₅N₂O₂S 441.1628 found 441.1637.}

1-methyl-2-(5-methylthiophen-2-yl)-3-(2-(phenylsulfonyl)phenyl)-2,3-dihydroquinazolin-4(1H)-one (109)



The title compound was prepared following the general protocol H using 2-(methylamino)-N-(2-(phenylsulfonyl)phenyl)benzamide (146 mg, 0.398 mmol), 5-methyl-2-thiophenecarbaldehyde (52 μ L, 0.476 mmol) and *p*-TSA (7 mg, 0.041). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 3/7) yielded the title compound (123 mg, 65%) as a white solid.

¹H-NMR (400MHz, DMSO-*d*₆) δ (ppm) = 2.29 (s, 3H), 2.94 (s, 3H), 6.04 (s, 1H), 6.54-6.58 (m, 1H), 6.70-6.86 (m, 4H), 7.11 (t, *J* = 7.8 Hz, 2H), 7.39-7.54 (m, 3H), 7.64-7.75 (m, 4H), 8.32 (dd, *J* = 7.6 Hz, *J'* = 1.9 Hz, 1H)

¹³C-NMR (100MHz, DMSO-*d*₆) δ (ppm) = 14.9, 35.0, 77.0, 112.6, 115.0, 117.7, 124.2, 127.6, 127.9, 128.6, 128.8, 129.3, 129.5, 133.1, 133.3, 134.6, 135.8, 137.5, 138.3, 139.2, 139.9, 146.2, 161.1

MS (ESI) [M+H]⁺ = 475.2

LC/MS (XBridge 100 \times 4.6 mm) : *t*_R = 8.30 min, *m/z* : 475.2 ([M+H]⁺)

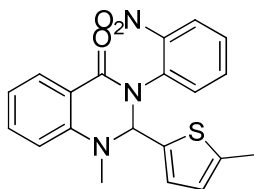
Gradient A : *t*_R = 23.82 min

Gradient D : *t*_R = 18.69 min

I.R. (neat, cm⁻¹) 3067, 2919, 2884, 1667, 1606, 1495, 1474, 1309, 1155, 738

HRMS *m/z* [(M+H)^{+ calcd for C₂₆H₂₃N₂O₃S₂ 475.1157 found 475.1150.}

1-methyl-2-(5-methylthiophen-2-yl)-3-(2-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (110)



The title compound was prepared following the general protocol H using 2-(methylamino)-N-(2-nitrophenyl)benzamide (109 mg, 0.402 mmol), 5-methyl-2-thiophenecarbaldehyde (52 μ L, 0.476 mmol) and *p*-TSA (7 mg, 0.041). The purification of the crude mixture by silica gel chromatography (EtOAc/cyclohexane 3/7) yielded the title compound (91 mg, 60%) as a white solid.

¹H-NMR (400MHz, DMSO-*d*₆) δ (ppm) = 2.32 (s, 3H), 2.92 (s, 3H), 6.43 (br s, 1H), 6.65 (br s, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.9 (t, *J* = 7.2 Hz, 2H), 7.08 (br s, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.75 (br s, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 8.06 (br s, 1H)

¹³C-NMR (100MHz, DMSO-*d*₆) δ (ppm) = 14.8, 35.1, 75.5, 113.5, 116.1, 118.5, 124.5, 124.9, 127.9, 128.2, 128.4, 132.6, 134.0, 134.8, 137.1, 139.9, 145.7, 146.8, 161.3

MS (ESI) [M+H]⁺ = 380.0

LC/MS (XBridge 100 \times 4.6 mm) : *t_R* = 7.83 min, *m/z* : 380.0 ([M+H]⁺)

Gradient A : *t_R* = 21.92 min

Gradient D : *t_R* = 18.77 min

I.R. (neat, cm⁻¹) 3071, 2919, 2885, 1662, 1604, 1530, 1493, 1354, 752

HRMS *m/z* [(M+H)^{+ calcd for C₂₀H₁₈N₃O₃S 380.1052 found 380.1069.}