Supporting Information

Quinine-thiourea catalyzed enantios elective hydrophosphonylation of trifluoromethyl 2(1H)-quinazolinones

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General Information: Commercial reagents were used as received, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence F_{254} were used for thin-layer chromatography (TLC) analysis. ¹H and ¹³C NMR spectra were recorded on Bruker Avance 500, and tetramethylsilane (TMS) was used as a reference. Data for ¹H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for ¹³C NMR are reported as ppm. Trifluoromethyl quinazolin-2(*1H*)-ones were prepared with reported method¹ and the other quinazolin-2(*1H*)-ones were prepared with Grignard reagents.²

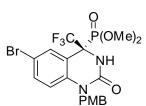
General procedure

To a mixture of quinazolin-2(1H)-one **1** (0.06 mmol) and catalyst (0.006 mmol) in solvent (0.5 mL) at rt was added dimethyl phosphite (0.12 mmol or 0.3 mmol). The resulting mixture was then stirred at rt until reaction completed. The pure product was obtained after purification by column chromatography on silica gel.



(*R*)-6-Chloro-1-(4-methoxybenzyl)-4-(dimethoxyphosphoryl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1H)-one (3a)

The title compound was prepared according to the general procedure, as described above in 91% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.77 (s, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 1H), 5.85 (s, 1H), 5.13 (d, *J* = 16.5 Hz, 1H), 5.05 (d, *J* = 16.5 Hz, 1H), 3.89 (d, *J* = 10.5 Hz, 3H), 3.77 (s, 3H), 3.73 (d, *J* = 10.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.9, 151.1 (d, *J* = 6 Hz), 136.7 (d, *J* = 7 Hz), 130.9, 128.3, 127.8, 127.5, 116.4, 114.3, 113.0 (d, *J* = 6 Hz), 55.4 (d, *J* = 7 Hz), 55.2, 54.8 (d, *J* = 7 Hz), 45.5; HPLC (Chiralcel OJ-H, *i*-PrOH/hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{minor} = 12.07 min, t_{major} = 20.20 min, ee = 89%; [α]_D²² = - 30.0 (*c* = 2.0 in CHCl₃).

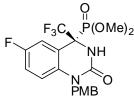


(*R*)-6-Bromo-1-(4-methoxybenzyl)-4-(dimethoxyphosphoryl)-4-(trifluoromethyl)-3,4dihydroquinazolin-2(1H)-one (3b)

The title compound was prepared according to the general procedure, as described above in 62% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.90 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 8 Hz, 2H), 6.85 (d, *J* = 8 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 1H), 5.79 (s, 1H), 5.13 (d, *J* = 16 Hz, 1H), 5.04 (d, *J* = 16 Hz, 1H), 3.89 (d, *J* = 11 Hz, 3H), 3.77 (s, 3H), 3.73 (d, *J* = 11 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 159.0, 151.0 (d, *J* = 6 Hz), 137.3, 133.9, 131.1, 127.7, 127.5, 116.8, 115.0, 114.3, 113.4, 55.4 (d, *J* = 7 Hz), 55.3, 54.9 (d, *J* = 7 Hz), 45.5; HPLC (Chiralcel OJ-H, *i*-PrOH/hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{minor} = 11.62 min, t_{major} = 19.45 min, ee = 90%; [α]_D²² = - 35.6 (*c* = 2.0 in CHCl₃).

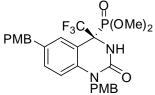
(*R*)-6-Iodo-1-(4-methoxybenzyl)-4-(dimethoxyphosphoryl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1H)-one (3c)

The title compound was prepared according to the general procedure, as described above in 62% yield. ¹H NMR (500 MHz, CDCl₃): δ 8.05 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 1H), 5.85 (s, 1H), 5.12 (d, *J* = 16.5 Hz, 1H), 5.03 (d, *J* = 16.5 Hz, 1H), 3.88 (d, *J* = 10.5 Hz, 3H), 3.77 (s, 3H), 3.73 (d, *J* = 10.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 159.0, 151.0 (d, *J* = 6 Hz), 139.8, 137.9 (d, *J* = 7 Hz), 136.8, 127.7, 127.5, 117.1, 114.3, 113.7, 84.7, 55.4 (d, *J* = 7 Hz), 55.3, 54.8 (d, *J* = 7 Hz), 45.4; HPLC (Chiralcel OJ-H, *i*-PrOH/hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{minor} = 12.84 min, t_{maior} = 21.45 min, ee = 87%; $\lceil \alpha \rceil_D^{22} = -37.6$ (*c* = 2.0 in CHCl₃).



(*R*)-6-Fluoro-1-(4-methoxybenzyl)-4-(dimethoxyphosphoryl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1H)-one (3d)

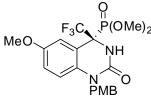
The title compound was prepared according to the general procedure, as described above in 75% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.57 (d, J = 9 Hz, 1H), 7.16 (d, J = 8 Hz, 2H), 7.00-6.97 (m, 1H), 6.86-6.81 (m, 3H), 5.87 (s, 1H), 5.13 (d, J = 16.5 Hz, 1H), 5.06 (d, J = 16.5 Hz, 1H), 3.89 (d, J = 10.5 Hz, 3H), 3.77 (s, 3H), 3.71 (d, J = 10.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.9, 158.6, 156.6, 151.2, 134.4, 127.9, 127.5, 117.9, 117.7, 116.5, 116.4, 115.8, 115.6, 114.3, 112.8, 55.3 (d, J = 7 Hz), 55.2, 54.8 (d, J = 7 Hz), 45.6; HPLC (Chiralcel OJ-H, *i*-PrOH/hexane = 40/60, flow rate = 0.6 mL/min, $\lambda = 254$ nm): t_{minor} = 11.69 min, t_{major} = 16.47 min, ee = 92%; [α]_D²² = - 3.5 (c = 2.0 in CHCl₃).



(*R*)-1,6-bis(4-Methoxybenzyl)-4-(dimethoxyphosphoryl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1H)-one (3e)

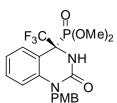
The title compound was prepared according to the general procedure, as described above in 85% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.65 (s, 1H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.06-7.03 (m, 3H), 6.84-6.76 (m, 5H), 5.78 (s, 1H), 5.11-5.02 (m, 2H), 3.85-3.82 (m, 5H), 3.76 (s, 6H), 3.50 (d, *J* = 10.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.8, 158.1, 151.4, 136.1 (d, *J* = 7 Hz), 135.9, 132.5, 131.0, 129.7, 128.8, 128.4, 127.6, 115.2, 114.2, 113.9, 111.2 (d, *J* = 6 Hz), 55.3, 55.2,

54.5 (d, J = 7 Hz), 45.4, 40.1; HPLC (ee was determined with the corresponding deprotection (PMB on the N) product. Chiralcel OJ-H, *i*-PrOH/hexane = 30/70, flow rate = 0.6 mL/min, $\lambda = 254$ nm): t_{minor} = 14.47 min, t_{major} = 18.01 min, ee = 93%; $[\alpha]_D^{22} = -9.9$ (c = 1.0 in CHCl₃).



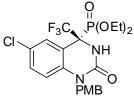
(*R*)-6-Methoxy-1-(4-methoxybenzyl)-4-(dimethoxyphosphoryl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1H)-one (3f)

The title compound was prepared according to the general procedure, as described above in 84% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.40 (s, 1H), 7.16 (d, J = 9 Hz, 2H), 6.85-6.78 (m, 4H), 5.83 (s, 1H), 5.11 (d, J = 16.5 Hz, 1H), 5.05 (d, J = 16.5 Hz, 1H), 3.88 (d, J = 10.5 Hz, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.66 (d, J = 10.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.8, 154.6, 151.3 (d, J = 6 Hz), 131.5 (d, J = 7 Hz), 128.4, 127.5, 116.4, 116.2, 114.2, 114.0, 112.2 (d, J = 6 Hz), 55.6, 55.3 (d, J = 7 Hz), 55.2, 54.6 (d, J = 7 Hz), 45.4; HPLC (Chiralcel OJ-H, *i*-PrOH/hexane = 40/60, flow rate = 0.6 mL/min, $\lambda = 254$ nm): t_{minor} = 13.18 min, t_{major} = 24.26 min, ee = 93\%; [α]_D²² = - 34.0 (c = 2.0 in CHCl₃).



(*R*)-1-(4-Methoxybenzyl)-4-(dimethoxyphosphoryl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1H)-one (3g)

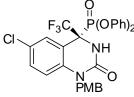
The title compound was prepared according to the general procedure, as described above in 88% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 8 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8 Hz, 1H), 6.85 (d, *J* = 8 Hz, 2H), 5.85 (s, 1H), 5.18-5.05 (m, 2H), 3.88 (d, *J* = 10.5 Hz, 3H), 3.77 (s, 3H), 3.63 (d, *J* = 10.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.8, 151.4 (d, *J* = 6 Hz), 138.0 (d, *J* = 7 Hz), 130.9, 128.6, 128.3, 127.5, 122.3, 115.2, 114.2, 111.2 (d, *J* = 6 Hz), 55.3 (d, *J* = 7 Hz), 55.2, 54.5 (d, *J* = 7 Hz), 45.3; HPLC (Chiralcel OJ-H, *i*-PrOH/hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{minor} = 11.05 min, t_{maior} = 16.80 min, ee = 93%; $\lceil \alpha \rceil_D^{22} = -15.9$ (*c* = 2.0 in CHCl₃).



(*R*)-6-Chloro-1-(4-methoxybenzyl)-4-(diethoxyphosphoryl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1H)-one (3h)

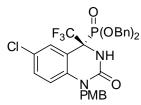
The title compound was prepared according to the general procedure, as described above in 84% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.80 (s, 1H), 7.21 (d, *J* = 9 Hz, 1H), 7.14 (d, *J* = 8.5 Hz,

2H), 6.84 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 9 Hz, 1H), 5.84 (s, 1H), 5.12 (d, J = 16 Hz, 1H), 5.05 (d, J = 16 Hz, 1H), 4.31-4.14 (m, 3H), 4.04-3.96 (m, 1H), 3.77 (s, 3H), 1.34 (t, J = 7 Hz, 3H), 1.20 (t, J = 7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.9, 151.1, 136.8 (d, J = 6 Hz), 130.7, 128.4, 127.8, 127.7, 127.5, 116.3, 114.3, 113.3, 65.3 (d, J = 7 Hz), 64.8 (d, J = 7 Hz), 55.2, 45.5, 16.3 (d, J = 5 Hz), 16.2 (d, J = 5 Hz); HPLC (Chiralcel OJ-H, *i*-PrOH/hexane = 40/60, flow rate = 0.6 mL/min, $\lambda = 254$ nm): t_{minor} = 8.34 min, t_{major} = 13.32 min, ee = 88%; $[\alpha]_D^{22} = -30.0$ (c = 2.0 in CHCl₃).



(*R*)-6-Chloro-1-(4-methoxybenzyl)-4-(diphenoxyphosphoryl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1H)-one (3j)

The title compound was prepared according to the general procedure, as described above in 97% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.86 (s, 1H), 7.30 (d, J = 8 Hz, 2H), 7.22-7.18 (m, 4H), 7.12-7.11 (m, 5H), 6.88 (d, J = 8 Hz, 2H), 6.80-6.77 (m, 3H), 6.37 (s, 1H), 5.10-5.02 (m, 2H), 3.75 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.9, 150.9 (d, J = 6 Hz), 150.1, 150.0, 149.7, 149.6, 136.9 (d, J = 7 Hz), 131.1, 130.0, 129.8, 128.7, 128.0, 127.6, 127.5, 126.0, 125.9, 120.3, 120.3, 120.0, 119.9, 116.5, 114.3, 112.1 (d, J = 6 Hz), 55.2, 45.7; HPLC (ee was determined with the corresponding deprotection (PMB) product. Chiralpak AS-H, *i*-PrOH/hexane = 40/60, flow rate = 0.6 mL/min, $\lambda = 254$ nm): t_{minor} = 10.28 min, t_{major} = 25.09 min, ee = 91%; [α]_D²² = - 32.8 (c = 2.0 in CHCl₃).

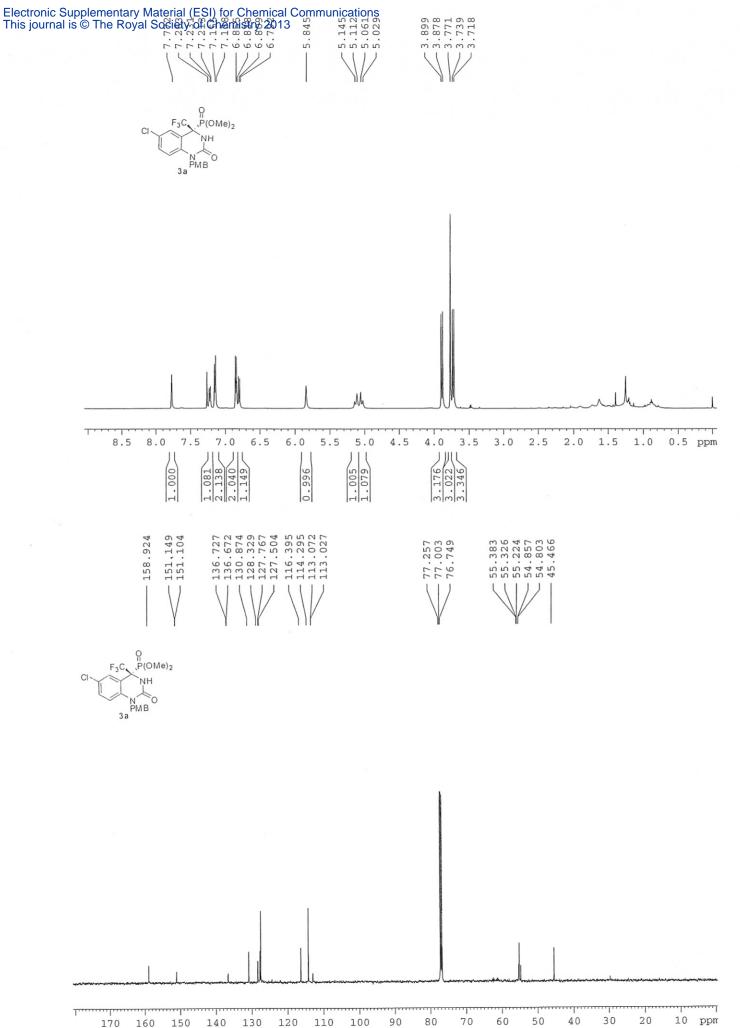


(*R*)-6-Chloro-1-(4-methoxybenzyl)-4-(dibenzyloxyphosphoryl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1H)-one (3j)

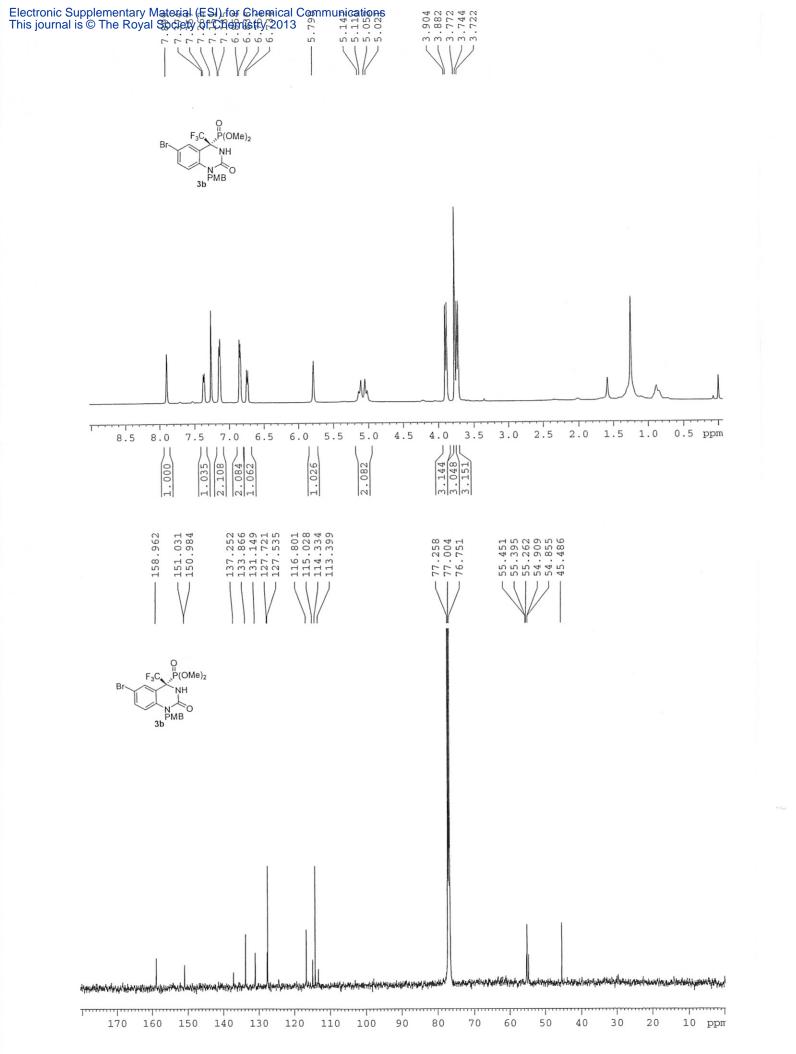
The title compound was prepared according to the general procedure, as described above in 84% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.80 (s, 1H), 7.35-7.24 (m, 8H), 7.16-7.10 (m, 3H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.64 (d, *J* = 9 Hz, 1H), 5.86 (s, 1H), 5.16-4.76 (m, 6H), 3.75 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.8, 150.9 (d, *J* = 6 Hz), 136.7 (d, *J* = 7 Hz), 134.8, 134.8, 130.7, 129.0, 128.8, 128.7, 128.6, 128.4, 127.8, 127.7, 127.4, 116.3, 114.3, 113.0 (d, *J* = 6 Hz), 70.2, 70.1, 70.1, 55.2, 45.4; HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 30/70, flow rate = 0.7 mL/min, λ = 254 nm): t_{minor} = 15.11 min, t_{major} = 17.86 min, ee = 81%; [α]_D²² = - 26.2 (*c* = 2.0 in CHCl₃).

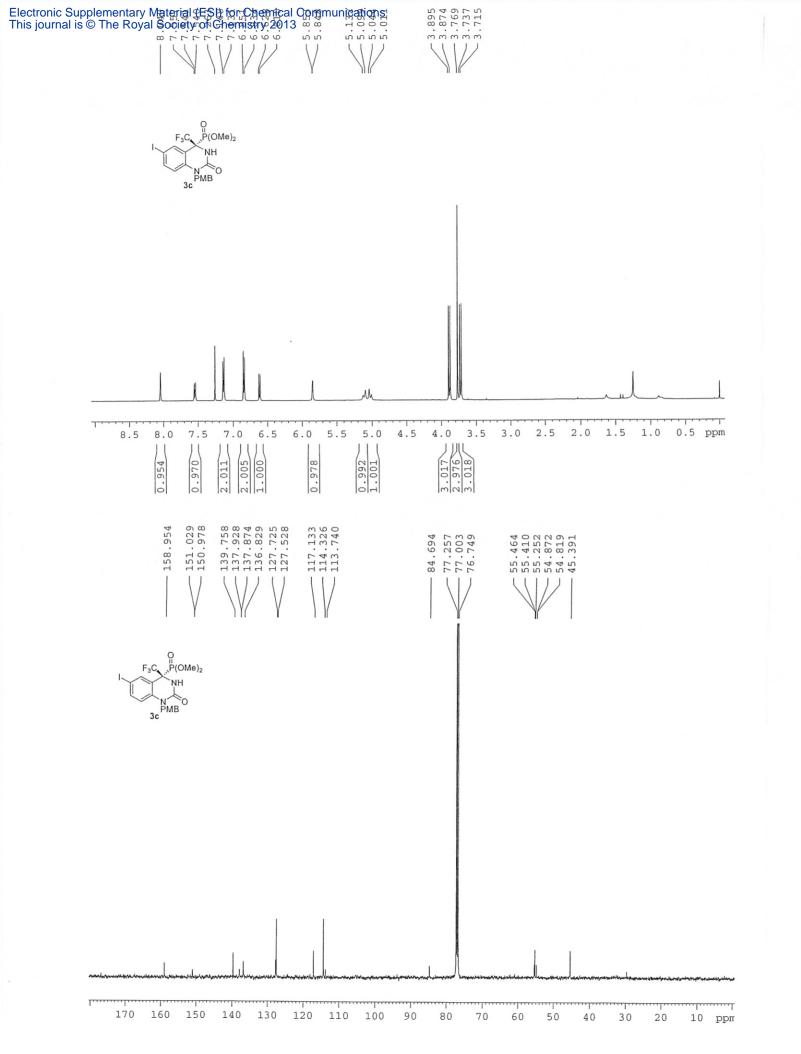
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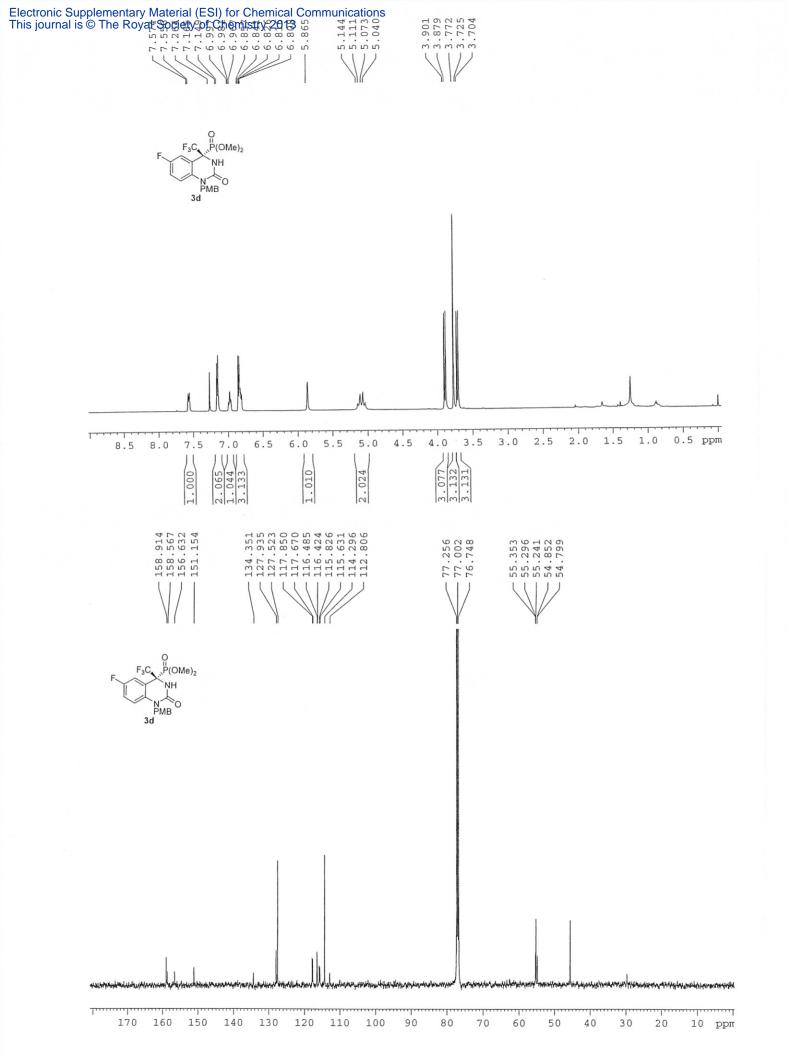
- 1. Magnus, N. A.; Confalone, P. N.; Storace, L.; Patel, M.; Wood, C. C.; Davis, W. P.; Parsons, Jr. R. L.; *J. Org. Chem.* **2003**, *68*, 754.
- 2. Bergman, J.; Brynolf, A.; Elman, B.; Vuorinen, E. Tetrahedron. 1986, 42, 3697.

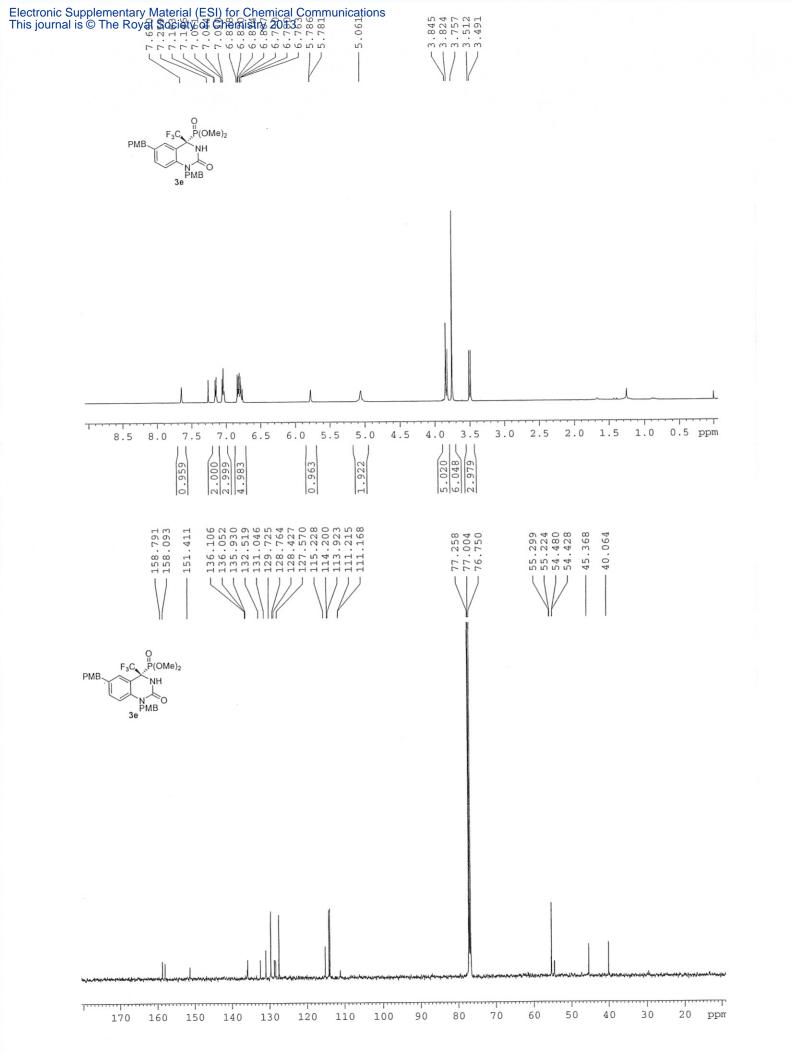


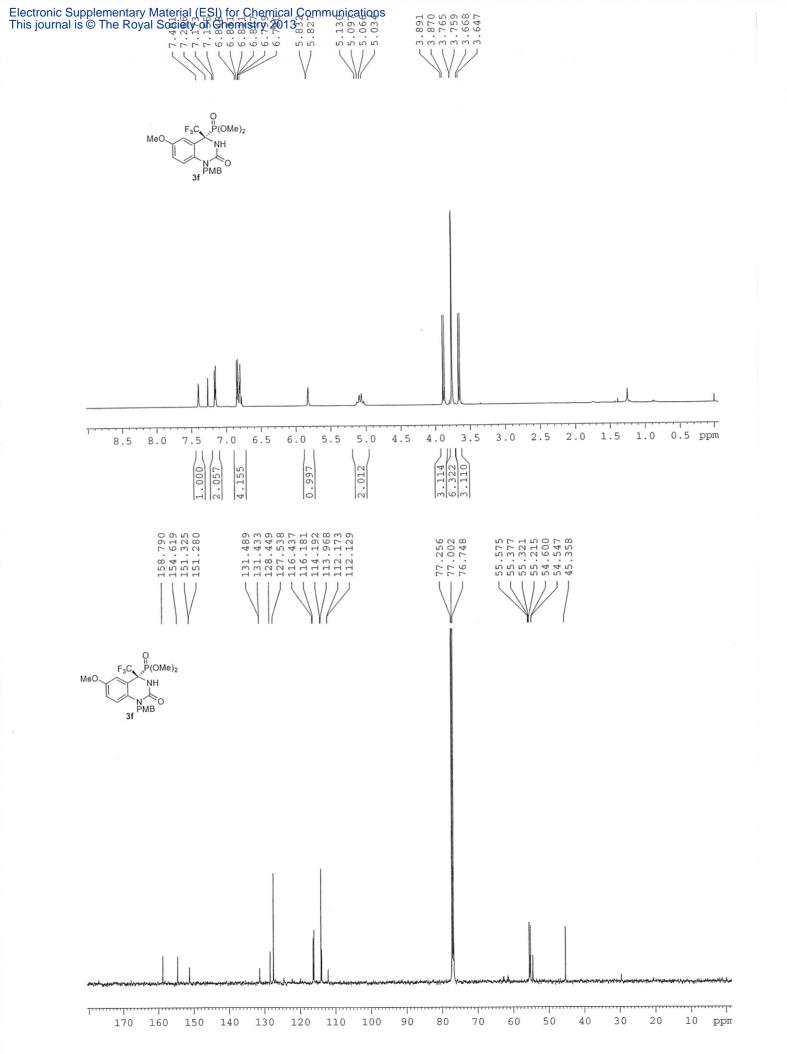
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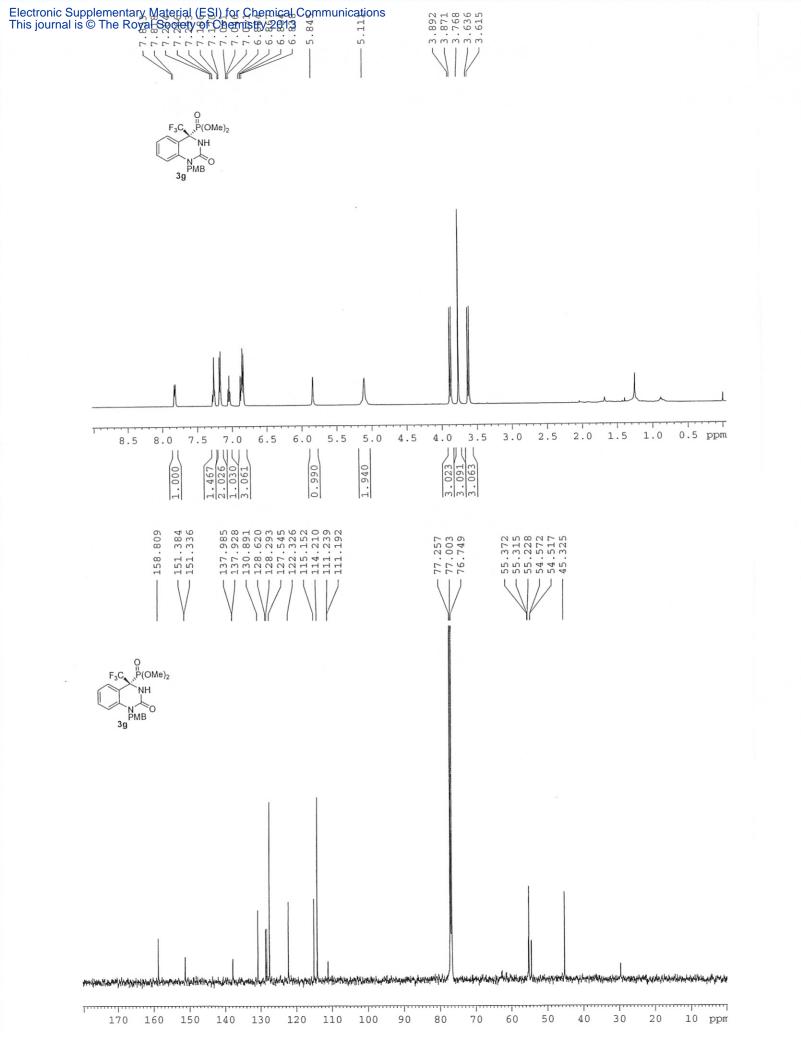


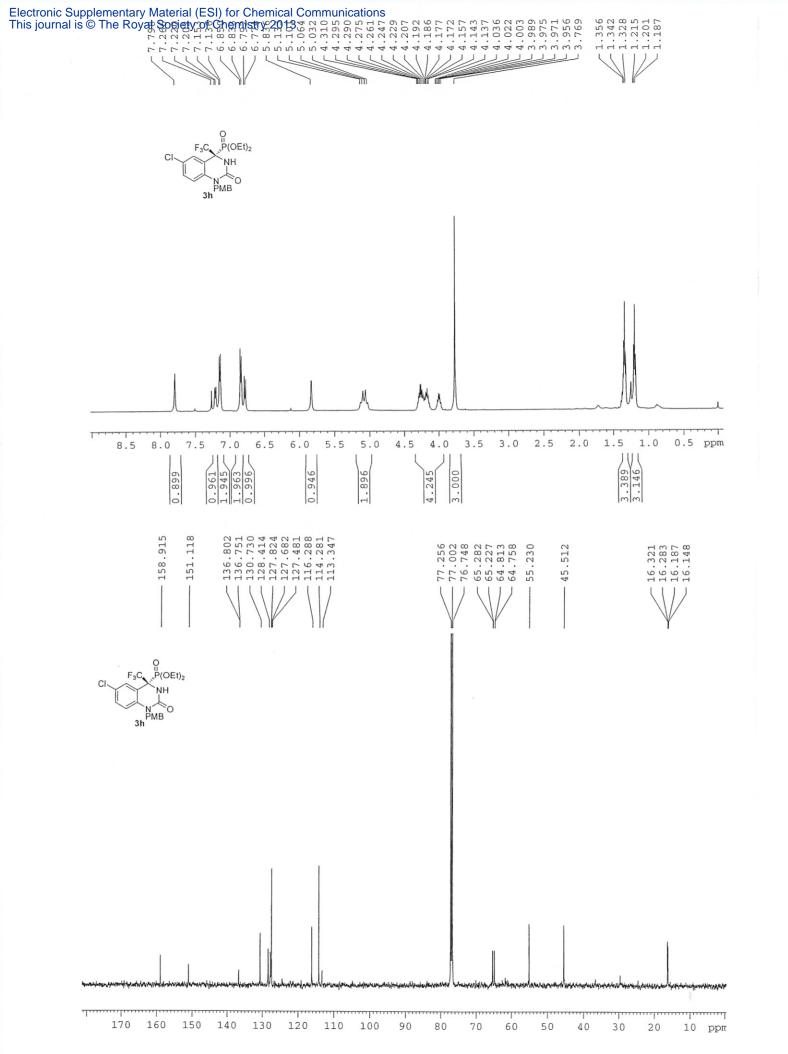


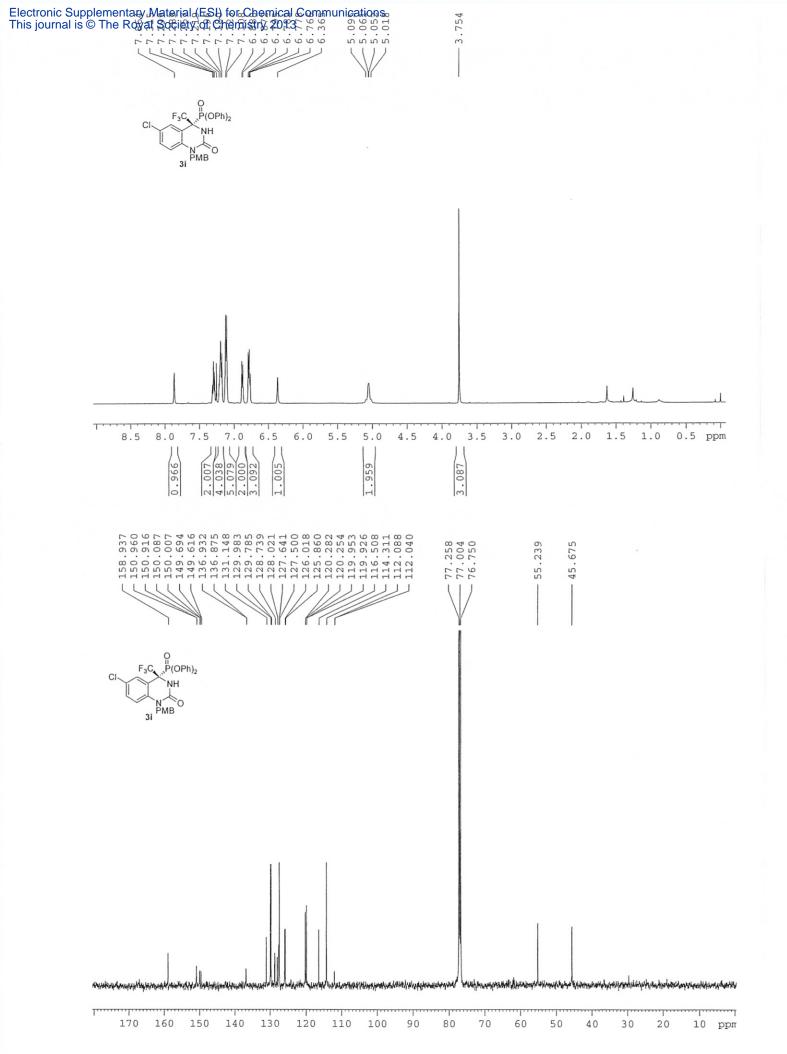


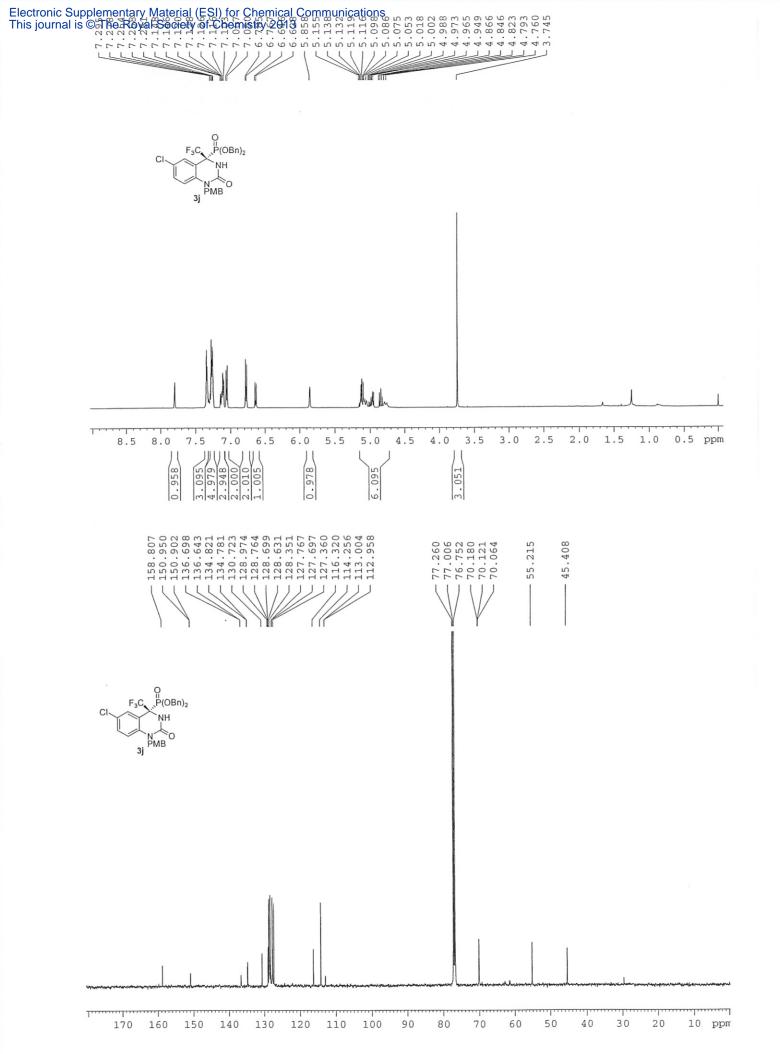


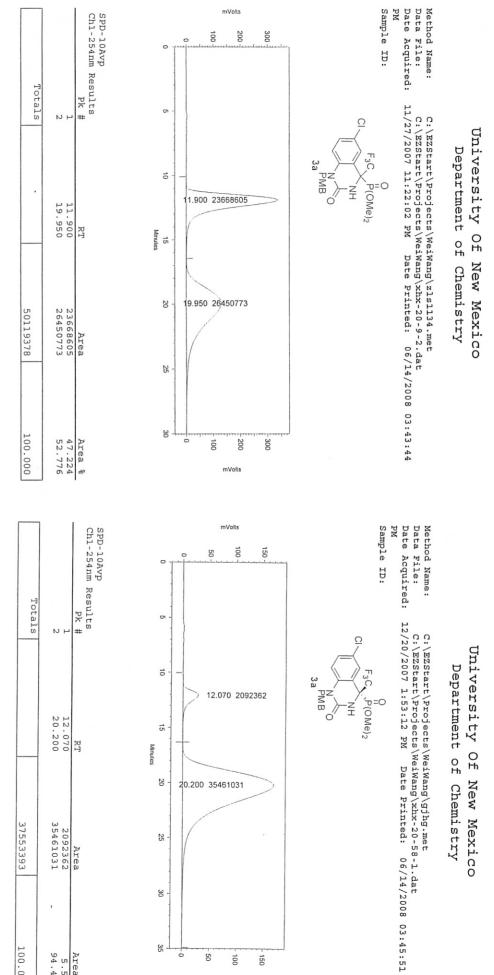






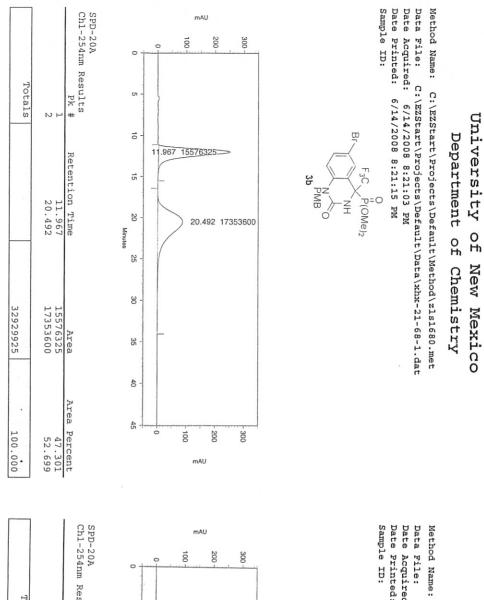






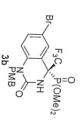
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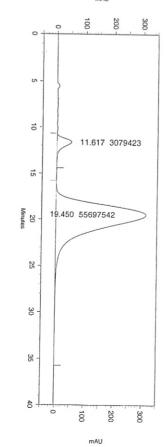
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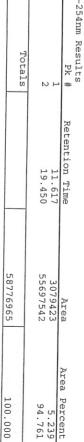


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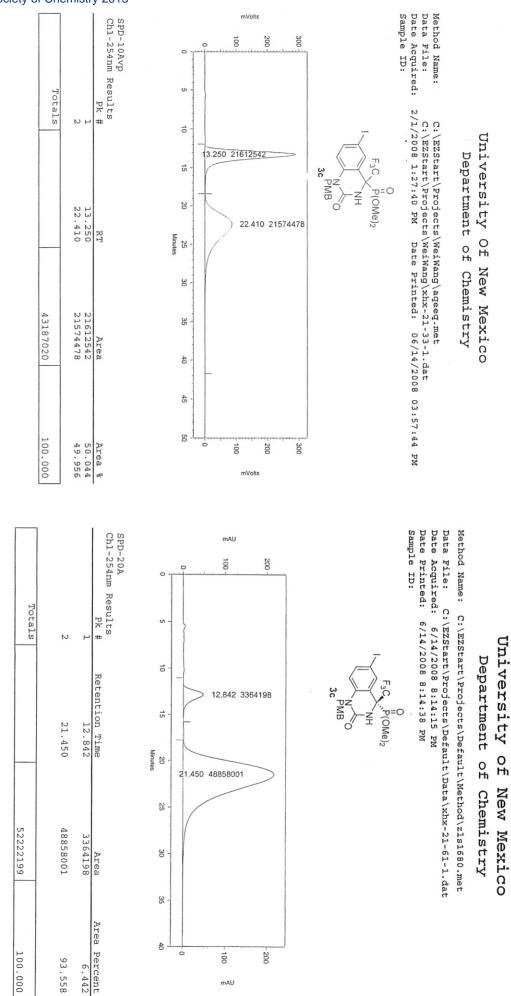
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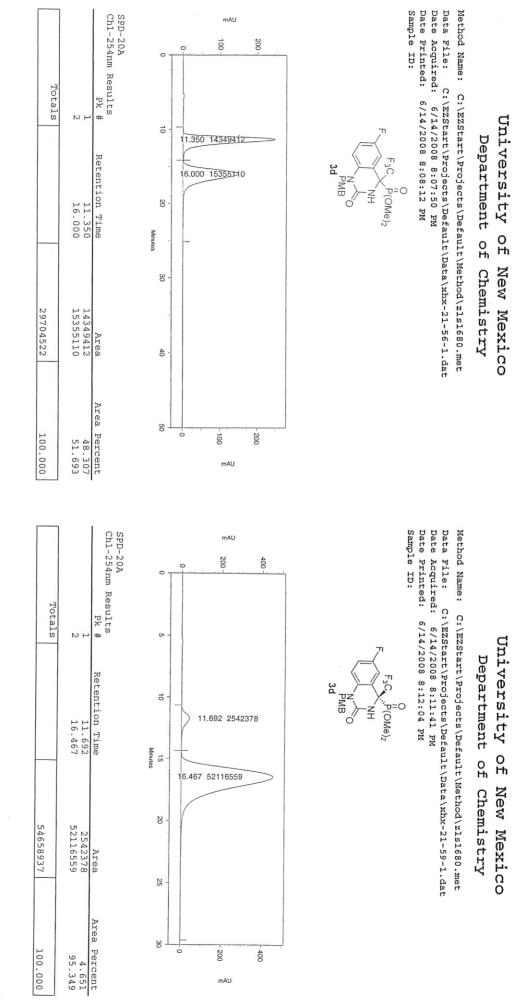


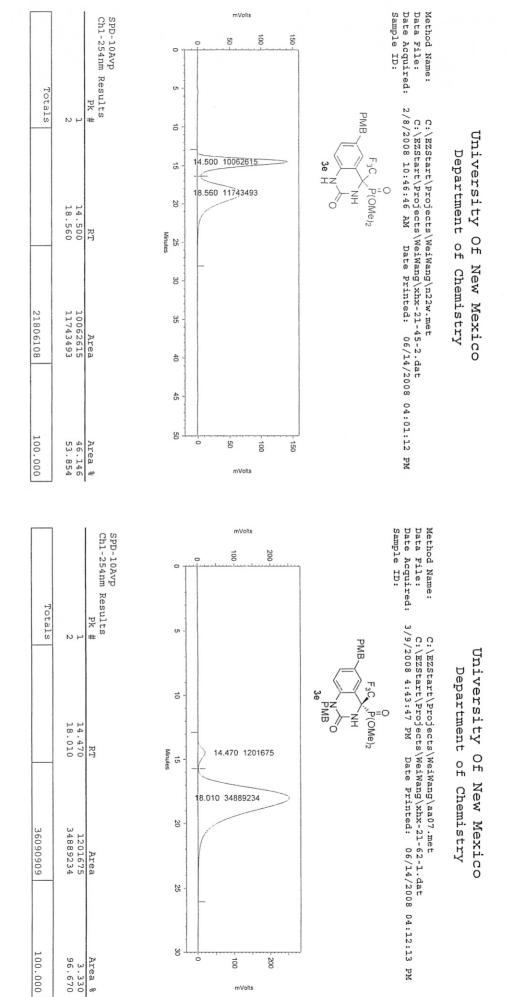


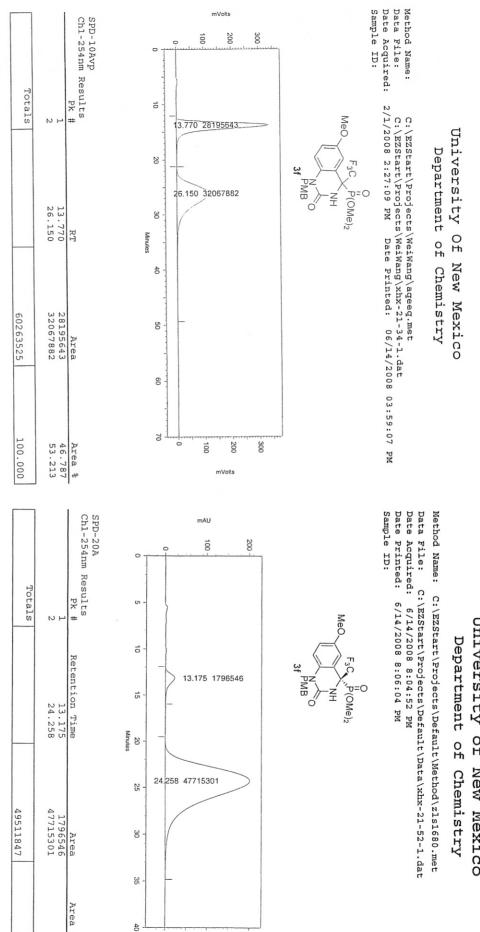
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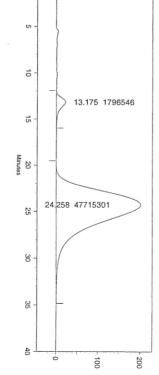
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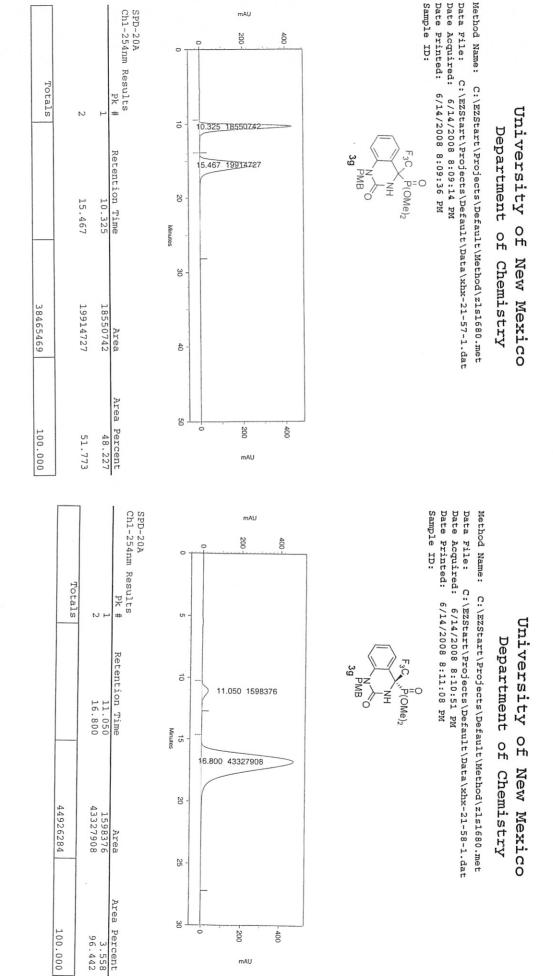


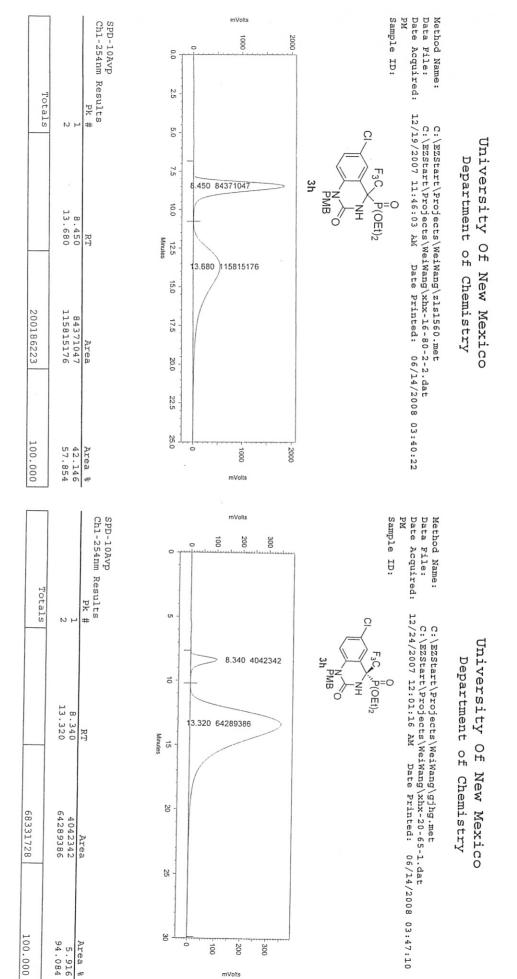
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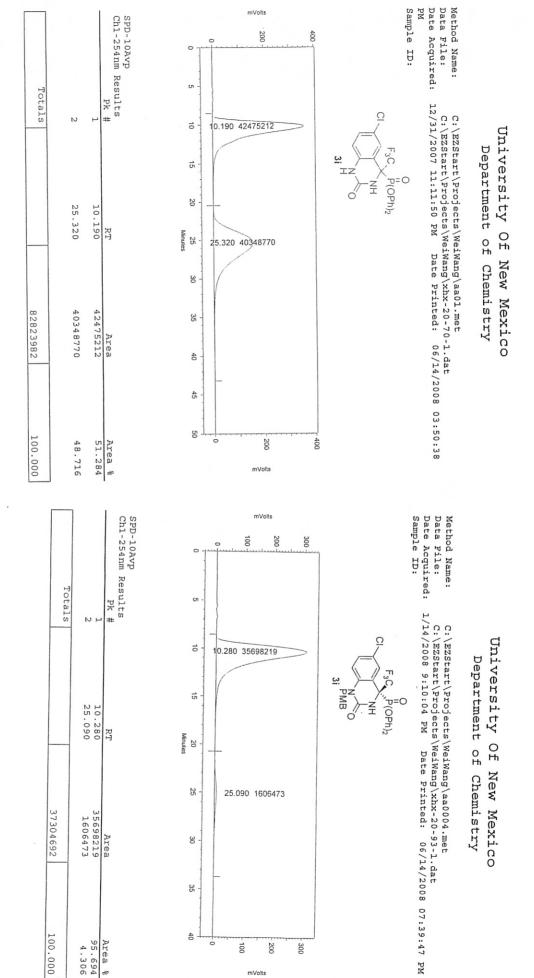


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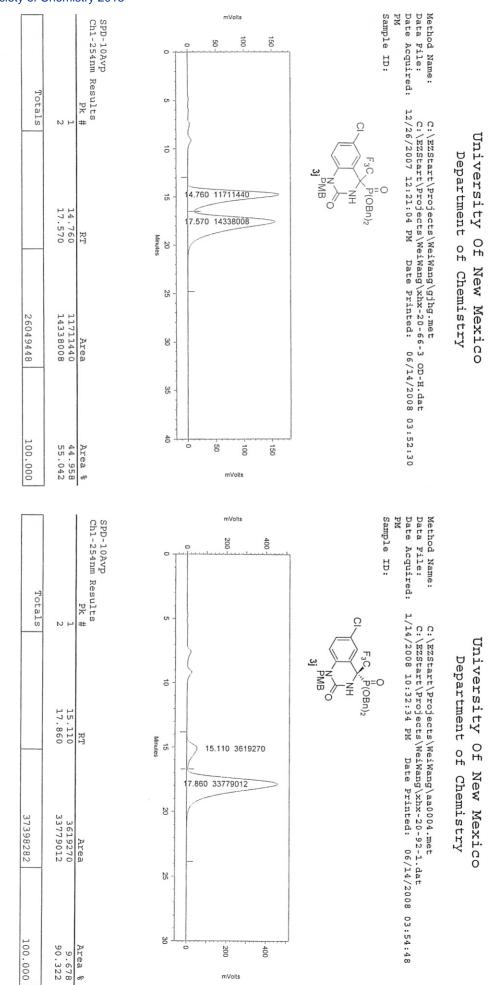
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mVolts



mVolts

Area %