Supporting Information for Substituted 2-Imino-5-arylidenethiazolidin-4-one Inhibitors of Bacterial Type III Secretion

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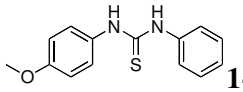
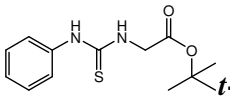
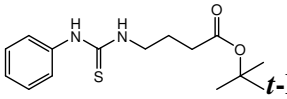
Contents



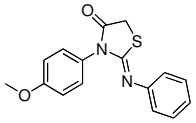
1-(4-methoxyphenyl)-3-phenylthiourea was prepared by **General method A** on a 4 mmol scale, using MeOH in place of CH_2Cl_2. Yield: 988 mg, 3.88 mmol. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.82 (s, 3H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.44-7.21 (m, 6H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 58.52, 117.81, 128.73, 129.41, 130.79, 132.48, 142.87, 162.12, 184.81. MS *m/z* 259 $[M + H]^+$, 281 $[M + Na]^+$.



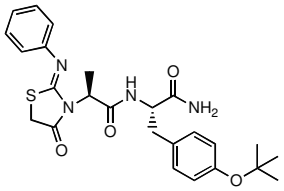
***t*-Butyl 2-(3-phenylthioureido)acetate** was prepared by **General method G** on a 1.19 mmol scale, but allowed to react for five hours to go to completion. Yield: 285 mg, 1.07 mmol. ^{1}H NMR (300 MHz, CD_3OD, δ): 1.50 (s, 9H), 4.25 (s, 2H), 7.12-7.45 (m, 5H). MS *m/z* 289 $[M + Na]^+$.



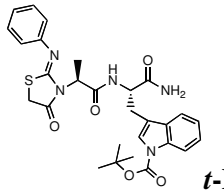
***t*-Butyl 4-(3-phenylthioureido)butanoate** was prepared by **method G** on a 1.53 mmol scale, and the crude material taken on without further purification. (^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.47 (s, 9H), 1.76-1.93 (m, 2H), 1.97-2.15 (m, 2H), 4.96-5.07 (m, 2H), 7.12-7.41 (m, 3H), 7.48 (t, *J* = 7.7 Hz, 2H), 8.01 (br s, 1H), 8.55 (br s, 1H). MS *m/z* 295 $[M + H]^+$, 317 $[M + Na]^+$.



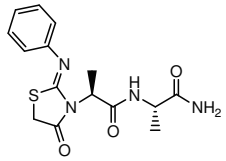
(*Z*)-3-(4-methoxyphenyl)-2-(phenylimino)thiazolidin-4-one was prepared by **General Method B** on a 1.64 mmol scale to give, after silica gel chromatography using a gradient from 0 to 5% MeOH in CH_2Cl_2, 487 mg, 1.63 mmol as a mixture of regiomers. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.82 (s, 3H, minor isomer), 3.87 (s, 3H, major isomer), 4.0 (s, 2H, major isomer), 4.02 (s, 2H, minor isomer), 6.90-7.16 (m, 4H, major and minor isomers), 7.29-7.57 (m, 5H, major and minor isomers). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 114.32, 114.72, 120.87, 121.94, 124.58, 127.19, 128.94, 129.03, 129.10, 129.34, 148.13, 159.71, 171.62. MS *m/z* 299 $[M + H]^+$, 321 $[M + Na]^+$.



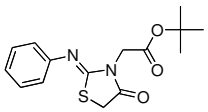
(S)-N-((S)-1-Amino-3-(4-*t*-butyoxyphenyl)-1-oxopropan-2-yl)-2-((Z)-4-oxo-2-(phenylimino)thiazolidin-3-yl)propionamide was prepared by **General method B** on a 0.20 mmol scale, using THF in place of CH_2Cl_2, to give, after silica gel chromatography using a gradient from 1 to 10 % MeOH in $CHCl_3$, 116 mg (0.20 mmol) product as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.33 (s, 9H) 1.55 (d, *J* = 11.5 Hz, 3 H), 3.02-3.26 (m, 2H), 3.73 (s, 2H), 4.71 (dd, *J* = 7.3, 6.6 Hz, 1H), 5.15 (dd, *J* = 7.2, 7.0 Hz, 1H), 5.00-5.50 (br, 1H), 6.05-6.07 (br, 2H), 6.91-7.36 (m, 9H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 17.51, 32.86, 36.64, 40.33, 56.74, 58.05, 82.54, 125.03, 128.18, 128, 44, 129.01, 132.01, 133.39, 133.51, 133.60, 133.79, 135.22, 51.26, 157.86, 172.47, 175.51, 177.25. MS *m/z* 483 $[M + H]^+$, 505 $[M + Na]^+$, 410 $[M - t\text{-Bu-OH} + H]^+$.



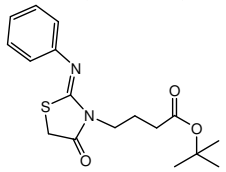
***t*-Butyl3-((S(-3-amino-3-oxo-2-((S)-2-((Z)-4-oxo-2-(phenylimino)thiazolidin-3-yl)propanamido)propyl)-1H-indole-1carboxylate** was prepared by **General method B** on a 0.13 mmol scale to give, after silica gel chromatography using a gradient from 1 to 10 % MeOH in $CHCl_3$, 39.6 mg (0.07 mmol) product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.57 (d, *J* = 7.0 Hz, 3H), 2.66 (s, 9H), 3.17-3.43 (m, 2H), 3.80 (d, *J* = 5.1 Hz, 2H), 4.86, (dd, *J* = 6.3, 7.6 Hz, 1H), 5.18 (q, *J* = 7.0 Hz, 1H), 5.40 (br, 1H), 6.49 (br, 1H), 6.61 (d, *J* = 8.5 Hz, 1H), 6.87 (d, *J* =12.5 Hz, 1H), 7.11-7.37 (m, 5H), 7.50 (s, 1H), 7.65 (d, *J* = 12.5 Hz, 1H), 8.15 (d, *J* = 12.6 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 17.49, 30.50, 32.22, 36.66, 56.68, 87.95, 119.18, 119.46, 122.96, 124.97, 126.94, 128.52, 128.88, 129.04, 133.39, 134.28, 139.50, 151.20, 153.54, 157.85, 172.46, 175.41, 176.90. MS *m/z* 550.3 $[M + H]^+$, 572.3 $[M + Na]^+$, 494 $[M - t\text{-Bu} + H]^+$, 516 $[M - t\text{-Bu} + Na]^+$.



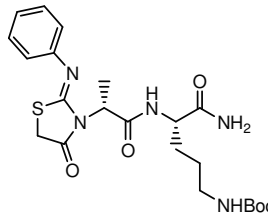
(S)-N-((S)-1-Amino-1-oxopropan-2-yl)-2-((Z)-4-oxo-2-(phenylimino)thiazolidin-3-yl)propanamide was prepared by **General Method B** in THF on a 1.49 mmol scale, but allowed to react 3 days to go to completion. The crude solid was purified via silica gel chromatography using a gradient from 1 to 10% MeOH in CH_2Cl_2 to give 300.0 mg, 0.90 mmol. ^{1}H NMR (500 MHz, CD_3OD, δ): 1.41 (d, *J* = 7.2 Hz, 3H), 1.67 (d, *J* = 7.0 Hz, 3H), 3.98 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 1H), 5.24 (q, *J* = 7.0 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (500 MHz, CD_3OD, δ): 16.45, 20.53, 36.45, 53.45, 56.65, 125.48, 129.06, 133.66, 152.77, 159.34, 175.10, 177.36, 181.31. MS *m/z* 357 $[M + Na]^+$.



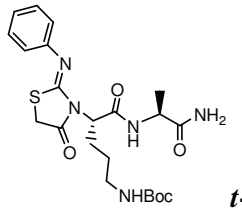
(Z)-*t*-Butyl 2-(4-oxo-2-(phenylimino)thiazolidin-3-yl)acetate was prepared by **General Method B** in THF on a 1.80 mmol scale to give, after silica gel chromatography using a gradient from 0 to 10% MeOH in CH_2Cl_2, 344.4 mg (1.12 mmol) product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.51 (s, 9H), 3.91 (s, 2H), 4.50 (s, 2H), 6.89-7.02 (m, 2H), 7.07-7.21 (m, 1H), 7.29-7.41 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 32.23, 37.03, 48.71, 87.14, 125.73, 129.49, 134.03, 152.51, 157.55, 170.89, 176.37. MS *m/z* 329 $[M + Na]^+$.



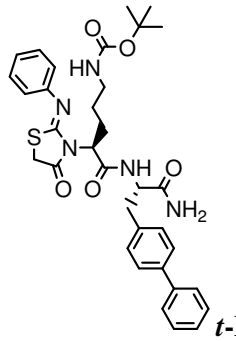
(Z)-*t*-Butyl 4-(4-oxo-2-(phenylimino)thiazolidin-3-yl)butanoate was prepared by **General method B** in THF, but allowed to react 2 days to go to completion. The crude solid was purified via silica gel chromatography using a gradient from 10 to 50% ethyl acetate in hexane to give **76** (246.2 mg, 0.74 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.47 (s, 9H), 1.64-1.96 (m, 4H), 3.75-3.83 (m, 2H), 4.02 (s, 2H), 7.33 (d, *J* = 7.04 Hz, 2H), 7.39 (d, *J* = 7.21 Hz, 1H), 7.48 (t, *J* = 7.35 Hz, 2H). MS *m/z* 335 $[M + H]^+$, 357 $[M + Na]^+$.



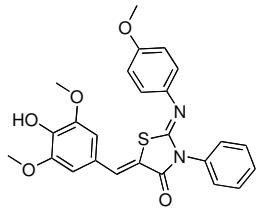
***t*-Butyl(S)-5-amino-5-oxo-4-((R)-2-((Z)-4-oxo-2-(phenylimino)thiazolidin-3-yl)propanamido)pentylcarbamate** was prepared **General method B** in THF on a 0.63 mmol scale, but allowed to react for 3 days to go to completion. The crude solid was purified via silica gel chromatography using a gradient from 0 to 10% MeOH in CH_2Cl_2 to give 277 mg (0.58 mmol) product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.44 (s, 9H), 1.50-1.71 (m, 3H), 1.73 (d, *J* = 7.1 Hz, 3H), 1.92-2.15 (m, 1H), 3.08-3.41 (m, 2H), 3.89 (d, *J* = 2.6 Hz, 2H), 4.56-4.80 (m, 1H), 5.19 (br s, 1H), 5.28 (q, *J* = 7.0 Hz, 1H), 6.80 (br s, 1H), 6.95 (d, *J* = 7.4 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.50 (br s, 2H). MS *m/z* 478 $[M + H]^+$, 500 $[M + Na]^+$.



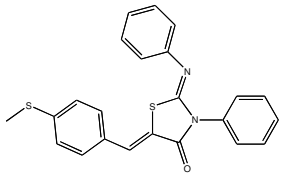
***t*-Butyl(S)-5-((S)-1-amino-1-oxopropan-2-ylamino)-5-oxo-4-((Z)-4-oxo-2-(phenylimino)thiazolidin-3-yl)pentylcarbamate** was prepared by **General method B** in THF on a 0.38 mmol scale, but allowed to react 4 days to go to completion. The crude solid was purified via silica gel chromatography using a gradient from 1 to 10% MeOH in $CHCl_3$ to give 109.7 mg (0.23 mmol) product. ^{1}H NMR (300 MHz, CD_3OD, δ): 1.39 (d, *J* = 7.2 Hz, 3H), 1.44 (s, 9H), 1.48-1.61 (m, 2H), 2.10-2.28 (m, 1H), 2.28-2.47 (m, 1H), 3.13 (t, *J* = 6.5 Hz, 2H), 4.00 (s, 2H), 4.46 (q, *J* = 7.2 Hz, 1H), 5.10-5.70 (m, 1H), 6.95 (d, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (500 MHz, CD_3OD, d): 20.62, 28.30, 29.62, 31.49, 36.26, 43.36, 53.09, 60.46, 82.59, 124.75, 128.37, 132.92, 151.87, 158.69, 161.19, 173.59, 176.85, 180.20. MS *m/z* 478 $[M + H]^+$, 500 $[M + Na]^+$.



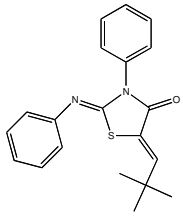
***t*-Butyl(S)-5-amino-N-((S)-1-amino-3-(biphenyl-4-yl)-1-oxopropan-2-yl)-2-((Z)-4-oxo-2-(phenylimino)thiazolidin-3-yl)pentanamide** was prepared by **General method B** in THF on a 0.082 mmol scale, but allowed to react 5 days to go to completion. The crude solid was purified via silica gel chromatography using a gradient from 1 to 10% MeOH in CH_2Cl_2 to give 47.5 mg (0.075 mmol) product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.39-1.64 (m, 11H), 1.96-2.20 (m, 1H), 2.20-2.41 (m, 1H), 3.00-3.36 (m, 4H), 3.77 (d, *J* = 6.1 Hz, 2H), 4.68-4.96 (m, 1H), 5.07-5.29 (m, 1H), 5.81 (br, 1H), 6.55 (br, 1H), 6.89 (d, *J* = 7.9 Hz, 2H), 7.09-7.24 (m, 1H), 7.24-7.74 (m, 11H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 28.69, 30.77, 32.45, 36.50, 40.92, 43.76, 58.34, 61.15, 83.39, 125.01, 129.04, 130.96, 131.37, 132.07, 132.83, 133.37, 133.73, 139.78, 143.83, 144.48, 151.16, 158.28, 160.16, 172.50, 175.85, 177.27. MS *m/z* 630 $[M + H]^+$, 652 $[M + Na]^+$.



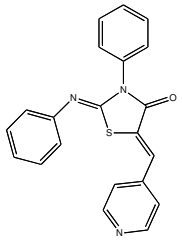
(2*Z*,5*Z*)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-2-(4-methoxyphenylimino)-3-phenylthiazolidin-4-one 26 was prepared by **General method C** from the regiomeric thiazolidinone mixture on a 0.15 mmol scale. Preparative reverse phase HPLC using a gradient of 60-80% B in A over 23 min enabled the separation of **26** (22.9 mg, 0.05 mmol) as one of the two regiomers as well as an overlap band that was held in reserve. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.31 (s, 3H), 2.33 (s, 6H), 4.03 (s, 2H), 4.18-4.30 (m, 4H), 4.39-4.44 (m, 5H), 4.64 (s, 1H). HRMS (*m/*z): $[M + H]^+$ calcd for $C_{25}H_{23}N_2O_5S$, 463.1322; found 463.1322; $[M + Na]^+$ calcd for $C_{25}H_{22}N_2NaO_5S$, 485.1142; found 485.1153.



(2*Z*,5*Z*)-5-(4-(methylthio)benzylidene)-3-phenyl-2-(phenylimino)thiazolidin-4-one 27 was prepared by **General method C** from the corresponding *bis*-phenylthiazolidin-4-one on a 0.075 mmol scale. Silica gel chromatography using a gradient of 0-20% ethyl acetate in hexane yielded **27** (14.51 mg, 0.036 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.53 (s, 3H), 7.02, (d, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.39-7.60 (m, 8H), 7.81 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 14.95, 119.90, 121.07, 124.83, 125.85, 128.03, 128.89, 129.25, 129.28, 129.41, 129.97, 130.35, 130.95, 134.71, 142.00, 148.26, 150.92, 166.50. HRMS (*m/*z): $[M + H]^+$ calcd for $C_{23}H_{19}N_2OS_2$, 403.0933; found 403.0926; $[M + Na]^+$ calcd for $C_{23}H_{18}N_2NaOS_2$, 425.0753; found 425.0744.

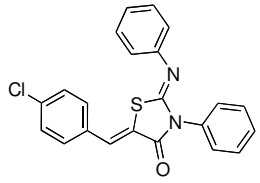


(2*Z*,5*Z*)-5-(2,2-dimethylpropylidene)-3-phenyl-2-(phenylimino)thiazolidin-4-one 28 was prepared by **General method C** from the corresponding *bis*-phenylthiazolidin-4-one on a 0.075 mmol scale. Silica gel chromatography using a gradient of 0-20% ethyl acetate in hexane yielded **28** (4.74 mg, 0.014 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.22 (s, 9H), 6.96-6.98 (m, 2H), 7.07-7.17 (m, 4H), 7.29-7.56 (m, 5H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 28.92, 29.01, 29.67, 29.70, 120.98, 121.07, 124.64, 124.76, 127.93, 128.04, 128.69, 128.80, 128.84, 129.08, 129.17, 129.20, 129.27, 129.42, 145.46, 157.60. HRMS (*m/*z): $[M + H]^+$ calcd for $C_{20}H_{21}N_2OS$, 337.1369; found 337.1361; $[M + Na]^+$ calcd for $C_{20}H_{20}N_2NaOS$, 359.1189; found 359.1180.

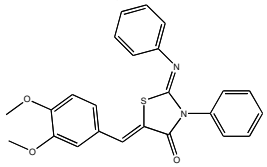


(2*Z*,5*Z*)-3-Phenyl-2-(phenylimino)-5-(pyridin-4-ylmethylene)thiazolidin-4-one 29 was prepared by **General method C** from the corresponding *bis*-phenylthiazolidin-4-one

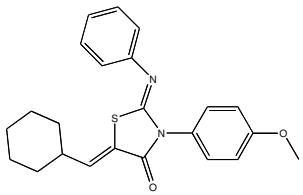
(*Erol, S.; Dogan, I., Axially chiral 2-arylimino-3-aryl-thiazolidine-4-one derivatives: enantiomeric separation and determination of racemization barriers by chiral HPLC. J Org Chem* ***2007,*** *72, (7), 2494-500)* on a 0.075 mmol scale. Silica gel chromatography using a gradient of 0-50% ethyl acetate in hexane yielded **35** (5.63 mg, 0.016 mmol). ^{1}H NMR (300 MHz, $CDCl_3$,d): 7.00 (d, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.36-7.43 (m, 5H), 7.50-7.61 (m, 5H), 7.75 (s, 2H), 8.72 (br, 2H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 29.71, 29.80, 120.91, 123.34, 123.38, 125.24, 126.71, 127.91, 127.96, 129.19, 129.38, 129.41, 134.37, 140.79, 147.79, 150.54. HRMS (*m/*z): $[M + H]^+$ calcd for $C_{21}H_{16}N_3OS$, 358.1009; found 358.1001; $[M + Na]^+$ calcd for $C_{21}H_{15}N_3NaOS$, 380.0828; found 380.0819.



(2*Z*,5*Z*)-5-(4-Chlorobenzylidene)-3-phenyl-2-(phenylimino)thiazolidin-4-one 30 was prepared by **General method C** from the corresponding *bis*-phenylthiazolidin-4-one on a 0.075 mmol scale. Silica gel chromatography using a gradient of 0-35% ethyl acetate in hexane yielded **36** (1.07 mg, 0.0027 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.97 (d, *J* = 7.3 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.35-7.57 (m, 10H), 7.77 (s, 2H). ^{13}C NMR (500 MHz, $CDCl_3$d): 121.03, 125.00, 128.01, 129.03, 129.32, 129.36, 130.00, 131.13. HRMS (*m/*z): $[M + H]^+$ calcd for $C_{22}H_{16}ClN_2OS$, 391.0666; found 391.0677; $[M + Na]^+$ calcd for $C_{22}H_{15}ClN_2NaOS$, 413.0486; found 413.0497.

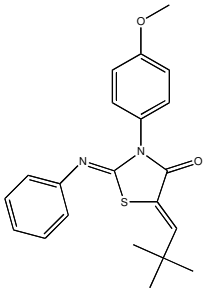


(2*Z*,5*Z*)-5-(3,4-Dimethoxybenzylidene)-3-phenyl-2-(phenylimino)thiazolidin-4-one 31 was prepared by **General method C** from the corresponding *bis*-phenylthiazolidin-4-one on a 0.075 mmol scale. Silica gel chromatography using a gradient of 0-30% ethyl acetate in hexane yielded **31** (11.63 mg, 0.028 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, δ): (s, 3H), 3.91 (s, 3H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.98-6.99 (m, 3H), 7.10-7.12 (m, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.44-7.56 (m, 5H), 7.77 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 33.76, 60.05, 60.13, 115.37, 117.30, 122.91, 125.17, 127.45, 128.86, 130.74, 132.06, 132.13, 132.94, 133.02, 133.15, 133.26, 133.35, 135.57, 138.84, 152.34, 153.20, 154.70, 155.14, 170.63. HRMS (*m/*z): $[M + H]^+$ calcd for $C_{24}H_{21}N_2O_3$, 417.1267; found 417.1247; $[M + Na]^+$ calcd for $C_{24}H_{20}N_2NaO_3S$, 439.1087; found 439.1068.

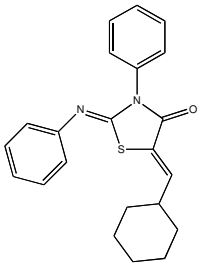


(2*Z*,5*Z*)-5-(Cyclohexylmethylene)-3-(4-methoxyphenyl)-2-(phenylimino)thiazolidin-4-one 32 was prepared by **General method C** from the regiomeric thiazolidinone mixture on a 0.067 mmol scale. Preparative reverse phase HPLC using a gradient of 80-95% B in A over 25 min enabled the separation of **32** (4.39 mg, 0.011 mmol) as one of the two regiomers as well **36** (16.88 mg, 0.043 mmol) as a ~1:1 mixture of regiomers. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.24 (s, 6H), 1.65 (s, 4H), 2.08 (s, 1H), 3.84 (s, 3H), 6.84 (d, *J* = 9.6 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.32-7.34 (m, 4H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 25.25, 25.56, 31.15, 41.06, 55.14, 114.64, 121.08, 122.74, 124.69,

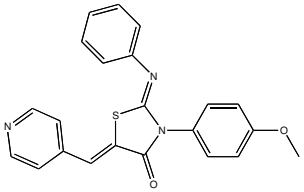
127.24, 129.06, 129.14, 140.50, 148.62, 159.63. HRMS (*m/*z): $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_2S$, 393.1631; found 393.1617; $[M + Na]^+$ calcd for $C_{23}H_{24}N_2NaO_2S$, 415.1451; found 415.1434.



(2*Z*,5*Z*)-5-(2,2-Dimethylpropylidene)-3-(4-methoxyphenyl)-2-(phenylimino)thiazolidin-4-one 33 was prepared by **General method C** from the regiomeric thiazolidinone mixture on a 0.067 mmol scale. Preparative reverse phase HPLC using a gradient of 60-95% B in A over 25 min enabled the separation of **33** (4.00 mg, 0.011 mmol) as one of the two compounds as well as **40** (2.68 mg, 0.007 mmol) as a ~1:1 mixture of regiomers. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.19 (s, 9H), 3.84 (s, 3H), 6.93 (d, *J* = 7.4 Hz, 1H), 7.02-7.03 (m, 2H), 7.13 (t, *J* = 7.4 Hz, 2H), 7.34-7.31 (m, 5H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 29.15, 33.90, 55.46, 114.66, 120.34, 121.11, 124.62, 127.32, 128.05, 129.09, 129.14, 145.39, 148.34, 159.63, 166.73. HRMS (*m/*z): $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_2S$, 367.1475; found 367.1474; $[M + Na]^+$ calcd for $C_{21}H_{22}N_2NaO_2S$, 389.1294; found 389.1287.

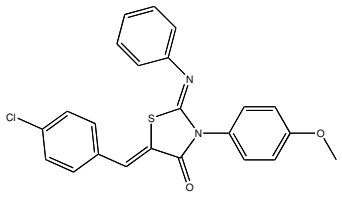


(2*Z*,5*Z*)-5-(Cyclohexylmethylene)-3-phenyl-2-(phenylimino)thiazolidin-4-one 34 was prepared by **General method C** from the corresponding *bis*-phenylthiazolidin-4-one[1] on a 0.089 mmol scale. Silica gel chromatography using a gradient of 0-10% ethyl acetate in hexane yielded **34** (9.64 mg, 0.027 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.26 (br, 6H), 1.74-1.57 (m, 4H), 2.09 (br, 1H), 6.85 (d, *J* = 9.6 Hz, 1H), 6.94 (d, *J* = 7.4 Hz, 3H), 7.13-7.16 (m, 2H), 7.33-7.53 (m, 5H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 25.26, 25.33, 25.59, 29.70, 31.16, 41.10, 121.04, 122.75, 124.73, 128.00, 128.85, 129.17, 129.26, 134.71, 140.59, 148.54, 151.52, 165.53. HRMS (*m/*z): $[M + H]^+$ calcd for $C_{22}H_{23}N_2OS$, 363.1526; found 363.1525; $[M + Na]^+$ calcd for $C_{22}H_{22}N_2NaOS$, 385.1345; found 385.1346.

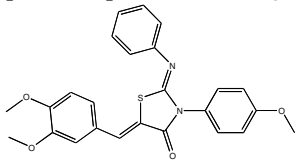


(2*Z*,5*Z*)-3-(4-Methoxyphenyl)-2-(phenylimino)-5-(pyridin-4-ylmethylene)thiazolidin-4-one 35 was prepared by **General method C** from the regiomeric thiazolidinone mixture on a 0.067 mmol scale. Preparative reverse phase HPLC using a gradient of 60-80% B in A over 25 min enabled the separation of **35** (3.17 mg, 0.008 mmol) as one of the two compounds as well as an additional 9.3 mg, 0.024 mmol, ~1:1 mixture of regiomers that was held in reserve. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.86 (s, 3H), 6.96 (d, *J* = 7.4 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 2H), 7.19-7.26 (m, 2H), 7.36-7.41 (m, 4H), 7.53-7.55 (m, 2H), 7.74 (s, 1H), 8.75 (s, 2H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 55.53, 114.81, 120.86, 124.41, 125.46, 125.99, 128.93,

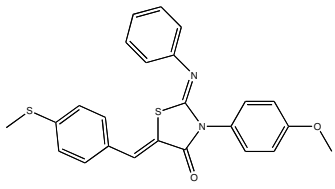
129.45, 147.06, 147.09. HRMS (*m/*z): [M + H]$^+$ calcd for $C_{22}H_{18}N_3O_2S$, 388.1114; found 388.1108; [M + Na]$^+$ calcd for $C_{22}H_{17}N_3NaO_2S$, 410.0934; found 410.0923.



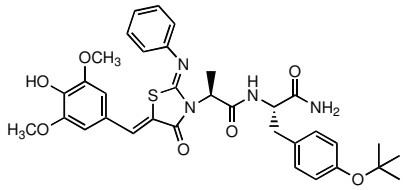
(2*Z*,5*Z*)-5-(4-Chlorobenzylidene)-3-(4-methoxyphenyl)-2-(phenylimino)thiazolidin-4-one 37 was prepared by **General method C** from the regiomeric thiazolidinone mixture on a 0.067 mmol scale. Preparative reverse phase HPLC using a gradient of 60-80% B in A over 25 min enabled the purification of, **37** (17.08 mg, 0.041 mmol) as a ~1:1 mixture of regiomers. ^{1}H NMR (300 MHz, $CDCl_3$, δ) : 3.83 (s, 3H, minor), 3.85 (s, 3H, major), 6.92 (s, 1H, major and minor), 6.96-7.07 (m, 3H, major and minor), 7.16-7.26 (m, 1H, major and minor), 7.35-7.58 (m, 7H, major and minor), 7.77 (s, 1H, major and minor). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 29.73, 55.46, 55.50, 114.53, 114.66, 114.73, 121.09, 122.18, 124.99, 128.00, 128.04, 128.76, 128.84, 128.86, 128.88, 128.90, 128.91, 128.95, 129.01, 129.11, 129.32, 129.36, 129.48, 129.52, 129.54, 129.57, 129.81, 129.89, 129.94, 131.14, 132.19, 135.85, 148.19, 150.96, 159.79, 166.48. HRMS (*m/*z): [M + H]$^+$ calcd for $C_{23}H_{18}ClN_2O_2S$, 421.0772; found 421.0775; [M + Na]$^+$ calcd for $C_{23}H_{17}ClN_2NaO_2S$, 443.0591; found 443.0591.



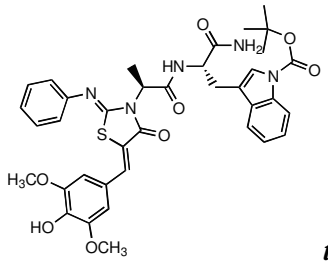
(2*Z*,5*Z*)-5-(3,4-Dimethoxybenzylidene)-3-(4-methoxyphenyl)-2-(phenylimino)thiazolidin-4-one 38 was prepared by **General method C** from the regiomeric thiazolidinone mixture on a 0.067 mmol scale. Preparative reverse phase HPLC using a gradient of 60-80% B in A over 23 min gave **38** (23.0 mg, 0.052 mmol) as a ~1:1 mixture of regiomers. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.85 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 6.90-7.19 (m, 8H), 7.33-7.40 (m, 4H), 7.77 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 55.48, 56.00, 111.32, 113.25, 114371, 121.20, 121.26, 123.40, 124.86, 126.69, 127.21, 129.16, 129.20, 129.25, 131.59, 148.23, 149.15, 150.66, 159.73, 166.83. HRMS (*m/*z): [M + H]$^+$ calcd for $C_{25}H_{23}N_2O_4S$, 447.1373; found 447.1366; [M + Na]$^+$ calcd for $C_{25}H_{22}N_2NaO_4S$, 469.1192; found 469.1190.



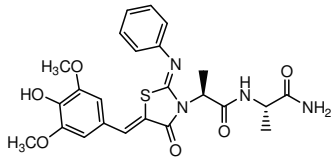
(2*Z*,5*Z*)-3-(4-Methoxyphenyl)-5-(4-(methylthio)benzylidene)-2-(phenylimino)thiazolidin-4-one 39 was prepared by **General method C** from the regiomeric thiazolidinone mixture on a 0.067 mmol scale. Preparative reverse phase HPLC using a gradient of 60-80% B in A over 23 min enabled the separation of additional **27** (6.24 mg, 0.014 mmol) as one of the two regiomers as well as **39** (3.47 mg, 0.0080 mmol) as a ~1:1 mixture of regiomers. ^{1}H NMR (300 MHz, $CDCl_3$, d): 2.50 (s, 3H), 3.85 (s, 3H), 6.91-7.23 (m, 7H), 7.34-7.41 (m, 6H), 7.77 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, d): 14.98, 55.47, 114.68, 121.12, 124.80, 125.88, 129.11, 129.24, 130.36, 130.89. HRMS (*m/*z): [M + H]$^+$ calcd for $C_{24}H_{21}N_2O_2S_2$, 433.1039; found 433.1041; [M + Na]$^+$ calcd for $C_{24}H_{20}N_2NaO_2S_2$, 455.0858; found 455.0865.



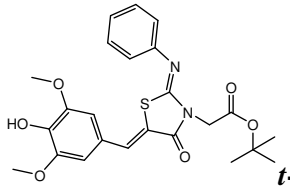
(*S*)-*N*-((*S*)-1-Amino-3-(4-*tert*-butoxyphenyl)-1-oxopropan-2-yl)-2-((2*Z*,5*Z*)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)propanamide was prepared by **General method C** on a 0.20 mmol scale to give 34 mg (0.05 mmol) product as a bright orange solid that was carried on to the deprotection step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.60 (d, *J* = 7.0 Hz, 3 H), 1.35 (s, 9H), 2.89 (br, 2H), 3.07 (dd, *J* = 6.6, 6.7 Hz, 1H), 3.33 (dd, *J* = 6.6, 6.7 Hz, 1H), 3.30 (br, 1H), 3.88 (s, 6H), 4.75 (q, *J* = 7.6, 6.6 Hz, 1H), 5.20 (br, 1H), 5.34 (dd, *J* = 7.0, 7.1 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 2H), 6.68 (s, 2H), 6.94-7.4 (m, 8H), 7.66 (s, 1H). MS *m/z* 647 $[M + H]^+$, 669 $[M + Na]^+$.



***t*-Butyl 3-((*S*)-3-amino-2-((*S*)-2-((2*Z*,5*Z*)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)propanamido)-3-oxopropyl)-1*H*-indole-1-carboxylate** was prepared by **General method C** on a 0.07 mmol scale to give, after purification on silica gel using a gradient from 0 to 20 % MeOH in CH_2Cl_2, 12 mg (0.02mmol) product as a bright orange solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.57-1.72 (s over m, 12H), 3.24-3,45 (m, 2H), 3.73 (s, 6H), 4.58-4.68 (m, 1H), 5.06-6.10 (m, 1H), 5.80-6.00 (br, 1H), 6.40-7.43 (m, 13H). MS *m/z* 714 $[M + H]^+$, 736 $[M + Na]^+$.

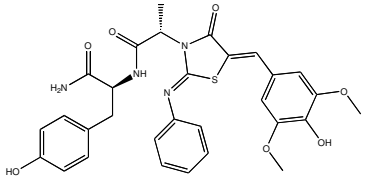


(S)-N-((S)-1-Amino-1-oxopropan-2-yl)-2-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)propanamide 41. Compound **41** was prepared by **General method C** on a 0.86 mmol scale. Preparative reverse phase HPLC on 20 mg crude material using a gradient from 10 to 60% B in A over 30 min gave **41** (3.5 mg, 0.007 mmol). ^{1}H NMR (500 MHz, CD_3OD, δ): 1.42, (d, *J* = 7.2 Hz, 3H), 1.73 (d, *J* = 7.0 Hz, 3H), 3.84 (s, 6H), 4.47 (q, *J* = 7.2 Hz, 1H), 5.42 (q, *J* = 7.0 Hz, 1H), 6.81 (s, 2H), 7.06 (d, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.71 (s, 1H). ^{13}C NMR (500 MHz, CD_3OD, δ): 16.66, 20.44, 53.21, 56.53, 59.44, 111.62, 121.77, 124.90, 128.46, 128.74, 133.03, 135.80, 142.28, 151.87, 152.20, 153.65, 170.45, 174.00, 180.30. MS *m/z* 499 $[M + H]^+$, 521 $[M + Na]^+$.

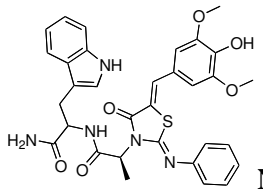


***t*-Butyl2-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)acetate** was prepared by **General method C** on a 1.12 mmol scale to give, after silica gel chromatography using a gradient from 10 to 50% ethyl acetate in

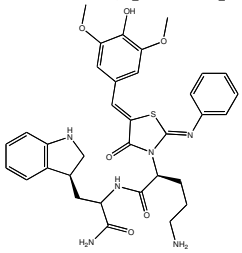
hexane, 329.8 mg (0.70 mmol) product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.52 (s, 9H), 3.89 (s, 6H), 4.64 (s, 2H), 6.71 (s, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 7.15-7.25 (m, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.72 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 32.06, 48.52, 60.48, 86.62, 111.25, 122.87, 125.20, 128.95, 129.26, 133.31, 136.01, 140.94, 151.29, 151.65, 153.62, 170.01, 170.40. MS *m/z* 471 $[M + H]^+$, 493 $[M + Na]^+$.



(S)-N-((S)-1-Amino-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-2-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)propanamide 43 was obtained by **General method D** on a 0.05 mmole scale and purified on reverse phase HPLC (20 to 95 % B in A over 12 min) to give the product (22 mg, 0.036 mmol) as the TFA salt. ^{1}H NMR (500 MHz, $(CD_3)_2CO$, d): 1.70 (d, *J* = 7.1 Hz, 3 H), 2.07 (br, 2H), 2.98 (dd, *J* = 7.7, 7.7 Hz, 1H), 3.09 (dd, *J* = 6.5, 6.5 Hz, 1H), 3.30 (br, 1H), 3.88 (s, 6H), 4.56 (br, 1H), 4.57 (q, *J* = 7.6, 5.8 Hz, 1H), 5.32 (dd, *J* = 7.0, 7.1 Hz, 1H), 6.50 (br, 1H), 6.73 (d, *J* = 8.4Hz, 2H), 6.89 (s, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.41 (m, 2H), 7.67 (s, 1H). MS *m/z* 591 $[M + H]^+$, 411 $[M - Tyr + H]^+$. HRMS (*m/*z): $[M + H]^+$ calcd for $C_{30}H_{31}N_4O_7S$, 591.1913; found 591.1905; $[M + Na]^+$ calcd for $C_{30}H_{30}N_4O_7NaS$, 613.1733; found 613.1719.

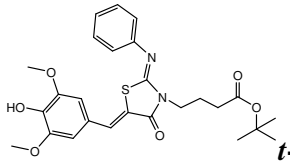


N-((S)-1-Amino-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)-2-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)propanamide 47a and **(R)-N-((S)-1-amino-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)-2-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)propanamide 47b** were obtained by **General method D** on a 0.04 mmole scale and purified on reverse phase HPLC (20 to 95 % B in A over 12 min) to give the products, as the TFA salts, from the earlier-eluting D,L-Ala L-Trp diastereomeric mix **47a** (2.7 mg, 0.004 mmol) ^{1}H NMR (500 MHz, CD_3OD, δ): 1.62 (dd, *J* = 6.6, 6.3 Hz, 3H), 3.25-3.32 (m, 2H), 3.83 (s, 6H), 4.60-4.65 (m, 1H), 5.25-5.38 (m, 1H), 6.75-8.10 (m, 13H); MS *m/z* 614 $[M + H]^+$, 636 $[M + Na]^+$, 411 $[M - Trp + H]^+$; HRMS (*m/*z): $[M + H]^+$ calcd for $C_{32}H_{31}N_5O_6S$, 614.2073; found 614.2072; $[M + Na]^+$ calcd for $C_{32}H_{31}N_5O_6NaS$, 636.1893; found 636.1881; and the later-eluting pure D-Ala L-Trp diastereomer **47b** (1.3 mg, 0.002 mmol). ^{1}H NMR (500 MHz, CD_3OD, δ): 1.60 (d, *J* = 7.0 Hz, 3H), 3.30-3.34 (m, 2H) , 3.85 (s, 6H), 4.62-4.64 (m, 1H), 5.28 (dd, *J* = 7.0, 7.1 Hz, 1H), 6.68-7.67 (m, 13H); MS *m/z* 614 $[M + H]^+$, 636 $[M + Na]^+$, 411 $[M - Trp + H]^+$; HRMS (*m/*z): $[M + H]^+$ calcd for $C_{32}H_{31}N_5O_6S$, 614.2073; found 614.2074; $[M + Na]^+$ calcd for $C_{32}H_{31}N_5O_6NaS$, 636.1893; found 636.1887; $[M + K]^+$ calcd for $C_{32}H_{31}N_5O_6KS$, 652.1632; found 652.1631.

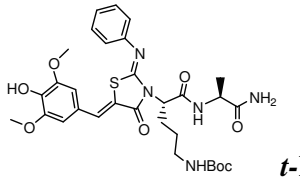


(*S*)-5-Amino-*N*-((*S*)-1-amino-3-(indolin-3-yl)-1-oxopropan-2-yl)-2-((5*Z*)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-

yl)pentanamide 49b The protected intermediate dipeptide (168 mg, 0.26 mmol) was dissolved in EtOH/DMF (2mL/2mL), and 10% palladium on carbon (150 mg) was added. Hydrogen gas was bubbled through the solution for 1 h, the catalyst was filtered off, and the filtrate concentrated *in vacuo*. The resulting residue was dissolved in MeOH and filtered through celite, rinsing with MeOH to fully remove the catalyst. After concentrating *in vacuo*, the residue was dissolved in 2 mL MeOH and phenylisothiocyanate (100 µL, 53 mmol,) was added. The reaction was stirred for 12h and then concentrated *in vacuo* to yield the thiourea that was dissolved in 5 mL THF, and diisopropylethylamine (90 µL, 0.52 mmol) and methyl bromoacetate (35 µL, 0.38 mmol) were added. After stirring for 12h, additional diisopropylethylamine (200 µL, 1.15mml) and methyl bromoacetate (100 µL, 1.09 mmol) were added and the reaction was let stir for another 24h. Added sat. NaCl (5 mL), $CHCl_3$ and rinsed the aqueous layer with $CHCl_3$ (3 x 5mL). The resulting organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was then purified via silica gel chromatography using a gradient from 1 to 6 % MeOH in CH_2Cl_2 to give the thiazolidinone (178 mg, 0.25 mmol) as a white solid. The protected 5-arylidene thiazolidinone was obtained via **General method C** on a 0.017 mmol scale. Silica gel chromatography using 0 to 6% MeOH in $CHCl_3$ gave 9.0 mg (0.010 mmol) of the penultilmate intermediate. **49b** was obtained from the protected 5-arylidene thiazolidnone (12.0 mg, 0.017 mmol) by **General method D**, and purified on reverse phase HPLC (10 to 60% B in A over 25 min) to give **49b** (1.66 mg, 0.0025 mmol) as the TFA salt. ^{1}H NMR (500 MHz, CD_3OD, δ): 1.19 (m, 2H), 1.64-1.80 (m, 2H), 1.95-2.18 (m, 2H), 2.33 (m, 2H), 2.88-2.98 (m, 2H), 3.53 (m, 2H), 3.71 (s, 6H), 3.86 (m, 1H), 4.58 (dd, *J* = 3.1 Hz, 1H), 5.40 (m, 1H), 6.65 (s, 2H), 6.95-7.30 (m, 9H), 7.59 (s, 1H). MS m/z 330 $[M + 2H]^{+2}$, 659 $[M + H]^+$. HRMS (*m/*z): $[M + H]^+$ calcd for $C_{34}H_{39}N_6O_6S$, 659.2652; found 659.2646; $[M + Na]^+$ calcd for $C_{34}H_{38}N_6NaO_6S$, 681.2471; found 681.2466.

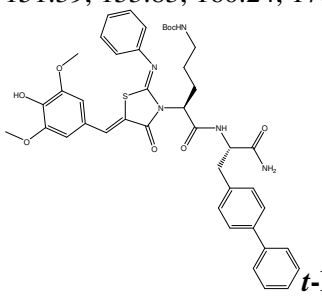


***t*-Butyl4-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)butanoate** was prepared by **General method C** on a 0.74 mmol scale to give, after silica gel chromatography using a gradient from 10 to 75% ethyl acetate in hexane, 190 mg (0.48 mmol) product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.48 (s, 9H), 1.73-2.01 (m, 4H), 3.81-3.93 (m, 2H), 3.99 (s, 6H), 6.84 (s, 2H), 7.36-7.62 (m, 5H), 7.75 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 14.48, 30.86, 32.08, 60.50, 71.33, 85.47, 111.28, 122.53, 129.48, 132.04, 132.45, 132.93, 135.21, 139.09, 140.83, 151.35, 154.28, 170.41, 174.38. MS *m/z* 499 $[M + H]^+$, 521 $[M + Na]^+$.

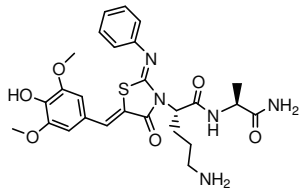


***t*-Butyl(S)-5-((S)-1-amino-1-oxopropan-2-ylamino)-4-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)-5-oxopentylcarbamate** was prepared by **General method C** on a 0.23 mmol scale to give, after silica gel chromatography using a gradient from 1 to 10% MeOH in $CHCl_3$, 117 mg (0.18 mmol) product. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 1.44 (s, 12H), 1.50-1.74 (m, 2H), 2.11-2.31 (m, 1H), 2.38-2.57 (m, 1H), 3.10-3.40 (m, 2H), 3.83 (s, 6H), 4.54-4.73 (m, 1H), 5.26-5.45 (m, 1H), 5.75 (br s, 1H), 6.61 (s, 2H), 6.80 (br s, 1H), 7.01 (d, *J* = 7.34 Hz, 2H), 7.14-7.29 (m, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.60 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 21.70, 29.16, 30.86, 32.43, 43.81, 53.00, 60.42, 61.21, 83.35, 111.41, 121.83, 125.17, 128.91, 129.22, 133.39, 136.66, 141.32,

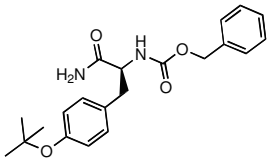
151.39, 153.83, 160.24, 170.80, 172.51, 178.70. MS *m/z* 642 $[M + H]^+$.



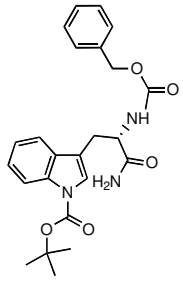
***t*-Butyl (S)-5-((S)-1-amino-3-(biphenyl-4-yl)-1-oxopropan-2-ylamino)-4-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)-5-oxopentylcarbamate** was prepared by **General method C** on a 0.075 mmol scale. The crude solid was purified via silica gel chromatography using a gradient from 0 to 5% MeOH in CH_2Cl_2 to give 41 mg (0.052 mmol). ^{1}H NMR (500 MHz, CD_3OD, δ): 1.41 (s, 9H), 1.46-1.66 (m, 2H), 2.12-2.29 (m, 1H), 2.34-2.52 (m, 1H), 3.00-3.21 (m, 3H), 3.21-3.32 (m, 1H), 3.71 (s, 6H), 4.62-4.75 (m, 1H), 5.24-5.40 (m, 1H), 6.64 (s, 2H), 6.90 (d, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.21-7.50 (m, 11H), 7.62 (s, 1H). ^{13}C NMR (500 MHz, CD_3OD, δ): 28.35, 30.27, 31.45, 40.66, 43.43, 58.66, 59.39, 60.76, 82.57, 111.62, 121.03, 125.00, 128.27, 128.73, 130.35, 130.74, 130.79, 132.32, 132.93, 133.33, 136.34, 140.12, 142.35, 143.37, 144.42, 151.55, 152.12, 153.72, 161.14, 170.61, 173.42, 178.71. MS *m/z* 795 $[M + H]^+$.



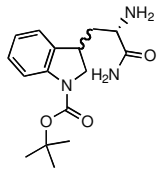
(S)-5-Amino-N-((S)-1-amino-1-oxopropan-2-yl)-2-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)pentanamide 45 was obtained by **General method D** on a 0.18 mmol scale and purified on reverse phase HPLC (10 to 75 % B in A over 30 min) to give 24.2 mg, 0.037 mmol as the TFA salt. ^{1}H NMR (300 MHz, CD_3OD, δ): 1.39 (d, *J* = 7.2 Hz, 3H), 1.62-1.94 (m, 2H), 2.38 (q, *J* = 8.0 Hz, 2H), 2.94-3.11 (m, 2H), 3.84 (s, 6H), 4.44 (q, *J* = 7.2 Hz, 1H), 5.37 (t, *J* = 7.4 Hz, 1H), 6.82 (s, 2H), 7.05 (d, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.74 (s, 1H). ^{13}C NMR (500 MHz, CD_3OD, δ): 20.70, 28.17, 28.77, 42.99, 53.25, 59.46, 59.99, 111.67, 121.37, 124.84, 128.36, 128.89, 133.07, 136.18, 151.65, 152.21, 153.65, 170.80, 173.07, 180.34. MS *m/z* 542 $[M + H]^+$. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{26}H_{32}N_5O_6S$, 542.2068; found 542.2071; $[M + Na]^+$ calcd for $C_{26}H_{31}N_5O_6NaS$, 564.1887; found 564.1888.



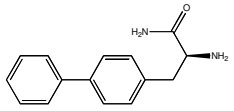
(S)–Benzyl-1-amino-3-(-4-*t*-butoxyphenyl)-1-oxopropan-2-ylcarbamate by **General method E.** on a 1 mmol scale from (S) Cbz tyrosine *t*-butyl ether DCHA salt to give, after chromatography, 393 mg, 1 mmol. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.36 (s, 9H), 3.02 (d, *J* = 6.0 Hz, 2H), 4.43 (m, 1H), 5.08 (s, 2H), 6.92 (d, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 7.5 Hz, 2H), 7.28-7.37 (m, 5H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 32.88, 41.86, 59.96, 70.98, 82.45, 128.28, 131.95, 132.18, 132.56, 133.83, 135.43, 140.24, 158.27, 160.24, 178.19. MS *m/z* 371 $[M + H]^+$, 393 $[M + Na]^+$.



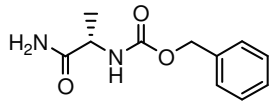
(*S*)-*t*-Butyl3-(3-amino-2-(benzyloxycarbonylamino)-3-oxopropyl)-1*H*-indole-1-carboxylate was prepared on a 1.6 mmol scale according to **General method E** to yield, after silica gel chromatography, 382 mg (0.87 mmol) product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.67 (s, 9H), 3.19-3.20 (m, 2H), 4.64-4.65 (m, 1H), 5.06 (s, 1H), 6.15-25 (br, 2H), 7.19-7.63 (m, 5H), 8.01-8.21 (br, 1H). MS *m/z* 438 $[M + H]^+$, 460 $[M + Na]^+$, 476 $[M + K]^+$, 420 $[M - t\text{-Bu} + H]^+$, 404 $[M - t\text{-Bu} + Na]^+$, 338 $[M - Boc + H]^+$, 338 $[M - Boc + Na]^+$.



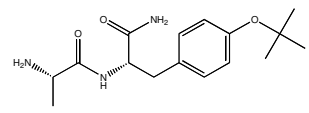
***t*-Butyl3-((S)-2,3-diamino-3-oxopropyl)indoline-1-carboxylate** was prepared on a 0.64 mmol scale from (S) Fmoc ±Dihydrotryptophan(Boc) according to **General method E** followed by N-α deprotection in 20% piperidine in DMF to yield, after silica gel chromatography, 102.89 mg (0.34 mmol) product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.24 (s, 9H), 1.53 (s, 9H), 1.78 (m, 1H), 2.01 (m, 2H), 2.22 (m, 1H), 2.61 (br, 2H), 3.52-3.67 (m, 6H), 4.12 (br, 2H), 6.89-6.92 (m, 4H), 7.13-7.16 (m, 4H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 28.33, 29.64, 36.46, 40.70, 52.99, 53.87, 114.70, 114.80, 122.32, 124.14, 127.92. MS *m/z* 306 $[M + H]^+$.



(S) 2-Amino-3-(biphenyl-4-yl)propanamide was prepared on a 0.66 mmol scale from Fmoc biphenylalanine according to **General method E** followed by deprotection in 20% piperidine in DMF to yield, after silica gel chromatography, 121 mg (0.50 mmol) product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.78 (dd, *J* = 9.5, 13.7 Hz, 2H), 3.31 (dd, *J* = 3.9, 13.7 Hz, 2H), 3.64-3.67 (m, 2H), 5.67 (br, 1H), 7.3-7.36 (m, 2H), 7.42-7.45 (m, 2H), 7.55-7.59 (m, 5H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 29.68, 40.53, 56.40, 126.96, 127.27, 127.44, 128.77, 129.70, 136.80, 139.82, 140.16. MS *m/z* 241 $[M + H]^+$.

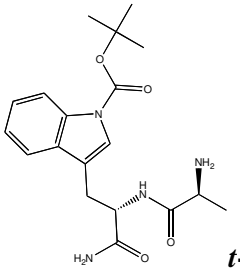


(S)-Benzyl 1-amino-1-oxopropan-2-ylcarbamate was prepared on a 2.0 mmol scale according to **General method E** to yield, with no further purification, 411 mg (1.85 mmol) product. ^{1}H NMR (300 MHz, CD_3OD, δ): 1.36 (d, *J* = 7.2 Hz, 3H), 4.15 (q, *J* = 7.2 Hz, 1H), 5.11 (s, 2H), 7.11-7.56 (m, 5H). MS *m/z* 245 $[M + Na]^+$.

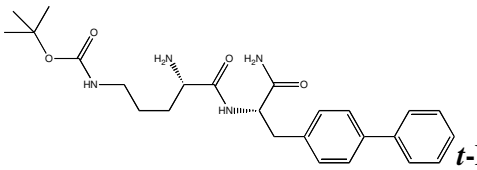


(S)-2-Amino-N-((S)-1-amino-3- (4-*t*-butoxyphenyl)-1-oxopropan-2-yl)propanamide was prepared by **General method F** from the N,O-protected tyramide (341 mg, 0.92 mmol) The catalyst was filtered off, and the filtrate concentrated *in vacuo* to give the free amine (173 mg, 0.73 mmol) ^{1}H NMR (500 MHz, CD_3OD, δ): 1.40 (s, 9H), 2.88 (dd, *J* = 7.7,

5.9 Hz, 1 H), 3.10 (dd, *J* = 7.9, 5.9 Hz, 1 H), 3.70 (dd, *J* = 6.8, 5.6 Hz, 1H), 7.02 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.24 (dd, *J* = 6.8, 1.5 Hz, 2H). MS *m/z* 237 $[M + H]^+$ that was coupled to Cbz-L-alanine to give the N,O-protected dipeptide (182 mg, 0.41 mmol) ^{1}H NMR (300 MHz, $(CD_3)_2CO$, δ): 1.29 (d, *J* = 7.2 Hz, 3H), 1.34 (s, 9H), 2.91 (dd, *J* = 8.3, 5.5 Hz, 1 H) , 3.13 (dd, *J* = 8.8, 5.1 Hz, 1H) , 4.11-4.16 (m, 1H), 4.58-4.65 (m, 1H), 5.07 (d, *J* = 5.8 Hz, 2H), 6.42 (br, 1H), 6.58 (br, 1H), 6.90 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.14 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.36-7.89 (m, 5H). MS *m/z* 442 $[M + H]^+$, 425 $[M - NH_2 + H]^+$, 386 $[M - t\text{-Bu} + H]^+$, 369 $[M - NH_2 - t\text{-Bu} + H]^+$ that was deprotected to the O-protected dipeptide (109 mg, 0.36 mmol) ^{1}H NMR (300 MHz, CD_3OD, δ): 1.15 (d, *J* = 7.0 Hz, 3H), 1.32 (s, 9H), 2.93 (dd, *J* = 8.9, 5.7 Hz, 1H) , 3.17 (dd, *J* = 8.1, 5.7 Hz, 1H), 3.40 (m, 1H), 4.61 (dd, *J* = 5.7, 3.2 Hz, 1H), 6.42 (br, 1H), 6.58 (br, 1H), 6.92 (dd, *J* = 6.5, 2.0 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.36-7.89 (m, 5H). MS *m/z* 308 $[M + H]^+$, 330 $[M + Na]^+$, 291 $[M - NH_2 + H]^+$, 263 $[M - C(CH_3) - NH_2 + H]^+$.

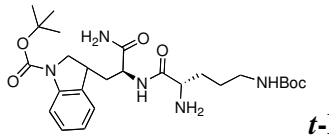


***t*-Butyl3-((*S*)-3-amino-2-((*S*)-2-aminopropanamido)-3-oxopropyl)-1*H*-indole-1-carboxylate** was prepared by **General method F** on a 0.83 mmol scale via the deprotection of N,N'-protected tryptophanamide to the free amine (220 mg, 0.73 mmol) ^{1}H NMR (300 MHz, CD_3OD, δ): 1.40 (s, 9H), 2.87-2.90 (m, 1H), 3.50-3.52 (m, 1H), 3,76 (m, 1H), 6.99-7.05 (m, 2H), 7.34 (s, 1H), 7.44-7.46 (m, 1H), 7.83-7.85 (m, 1H); MS *m/z* 304 $[M + H]^+$, followed by reaction to the protected dipeptide (153 mg, 0.30 mmol) ^{1}H NMR (300 MHz, $(CD_3)_2O$, δ): 1.33 (d, *J* = 7.1 Hz, 3H), 1.67 (s, 9H), 3.10 (dd, *J* = 7.8, 9.7 Hz, 1H), 3.28 (dd, *J* = 5.1, 9.7 Hz, 1H), 4.15-4.20 (m, 1H), 4.74 (dt, *J* = 5.5, 8.0, 5.5 Hz, 1H), 5.05 (d, *J* = 7.1 Hz, 2H), 6.49 (br, 2H), 7.03 (br, 1H), 7.25-7.72 (m, 10H), 8.14 (m, 1H); MS *m/z* 510 $[M + H]^+$, 532 $[M + Na]^+$, 475 $[M - t\text{-Bu} + Na]^+$; and finally hydrogenolysis to the α-amino protected dipeptide amide (90.0 mg, 0.24 mmol) ^{1}H NMR (300 MHz, CD_3OD, δ): 1.41(d, *J* = 6.9 Hz, 3H), 1.44 (s, 9H), 2.86-3.07 (m, 2H), 3.36 (q, *J* = 6.4 Hz, 1H), 4.50 (dd, *J* = 6.1, 6.0 Hz, 1H), 7.07-7.09 (m, 2H), 7.29 (s, 1H), 7.44-7.46 (m, 1H), 7.84-7.86 (m, 1H). ^{13}C NMR (500 MHz, CD_3OD, δ): 20.97, 29.78, 49.69, 52.16, 55.50, 86.03, 117.26, 118.51, 121.35, 124.84, 126.46, 126.64, 131.39, 132.86, 137.89, 152.11, 176.48, 177.05. MS *m/z* 375 $[M + H]^+$, 397 $[M + Na]^+$.

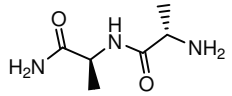


***t*-Butyl(S)-4-amino-5-((S)-1-amino-3-(biphenyl-4-yl)-1-oxopropan-2-ylamino)-5-oxopentylcarbamate** was prepared by **General method F**. Tetrahydrofuran (3 mL) was added to a dry mixture of Cbz L-ornithine (Boc) (27.6 mg, 0.075 mmol) and carbonyldiimidazole (15 mg, 0.093 mmol), and the reaction mixture was allowed to stir for 1 h. To this was added the biphenylalanine amide α-amine along with diisopropylethylamine (20 μL, 0.11 mmol), and the reaction mixture stirred for 18 h until determined complete by TLC (85:15 $CHCl_3$/MeOH). A saturated solution of $NaHCO_3$ (5 mL), water (15 mL), and chloroform (10 mL) were added and the layers were separated. The resulting organic layer was rinsed with a saturated solution of NaCl (10 mL), concentrated *in vacuo*, and purified on silica gel using a gradient from 0 to 10% MeOH in $CHCl_3$ to give the Cbz-protected

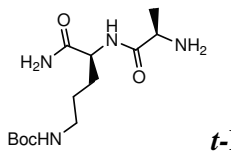
dipeptide (13.26 mg, 0.022 mmol) ^{1}H NMR (300 MHz, CD_3OD, δ): 0.29 (s, 9H), 0.35-0.55 (m, 2H), 0.45-0.65 (m, 2H), 1.86-1.94 (m, 4H), 2.59 (s, 2H), 2.92-2.95 (m, 1H), 3.07-3.09 (m, 1H), 3.54-3.57 (m, 1H), 3.92-3.98 (m, 2H), 6.18-6.29 (m, 9H), 6.38-6.44 (m, 5H). MS *m/z* 589 $[M + H]^+$ which was hydrogenated over 10% palladium on carbon (130 mg) in a mixture of 10 mL EtOH and 1.5 mL DMF for 4 h. The catalyst was filtered off and the filtrate concentrated *in vacuo* to give the free α-amino dipeptide (MS *m/z* 455.3 $[M + H]^+$) which was taken forward without further purification.



***t*-Butyl3-((S)-3-amino-2-(S)-2-amino-5-(*t*-butoxycarbonylamino)pentamido)-3-oxopropyl)indoline-1-carboxylate** was prepared by **General method F**. Tetrahydrofuran (3 mL) was added to a dry mixture of Cbz L-ornithine (Boc) (25.7 mg, 0.070 mmol) and carbonyldiimidazole (14 mg, 0.086 mmol) and the reaction mixture was allowed to stir for 1 h. To this was added the N^{ind}-protected dihydroindole amide α-amine, along with diisopropylethylamine (20 mL, 0.11 mmol), and the reaction mixture stirred for 18 hours until determined complete by TLC (85:15 $CHCl_3$/MeOH). A saturated solution of $NaHCO_3$ (5 mL), water (15 mL), and chloroform (10 mL) were added and the layers were separated. The resulting organic layer was rinsed with a saturated solution of NaCl (10 mL), concentrated *in vacuo*, and purified on silica gel using a gradient from 0 to 10% MeOH in $CHCl_3$ to give the protected intermediate which, upon hydrogenolysis, gave the α-amine dipeptide (17.68 mg, 0.026 mmol). ^{1}H NMR (300 MHz, CD_3OD, δ): 0.28 (s, 9H), 0.43 (s, 9H), 0.69-0.80 (m, 2H), 0.94-1.05 (m, 2H), 1.93 (t, *J* = 6.5 Hz, 2H), 2.22 (s, 2H), 2.42-2.6 (m, 2H) 3.33-3.45 (m, 2H), 3.89-3.96 (m, 2H), 5.81-5.83 (m, 2H), 6.02-6.17 (m, 7H), 6.21-6.60 (br, 1H). MS *m/z* 654 $[M + H]^+$.

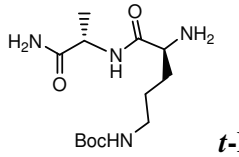


(S)-2-Amino-N-((S)-1-amino-1-oxopropan-2-yl)propanamide Cbz-L-alanine (669 mg, 3 mmol) and L-alaninamide (376 mg, 3 mmol) were coupled by the carbonyldiimidazole method to give the protected dipeptide (891 mg, 3.0 mmol). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.41 (d, *J* = 7.1 Hz, 6H), 4.21 (t, *J* = 7.2 Hz, 1H), 4.20 (t, *J* = 7.2 Hz, 1H), 5.03 (d, *J* = 3.3 Hz, 2H), 7.02 (s, 2H), 7.30-7.38 (m, 5H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (500 MHz, DMSO-d_6, δ): 22.52, 22.92, 52.35, 54.60, 69.85, 132.17, 132.26, 132.83, 141.48, 176.44, 178.57. MS *m/z* 316 [M + Na]. The protected dipeptide was hydrogenated over 10% palladium on carbon (420 mg) in 1:1 EtOH/DMF (55 mL) for 3 h. The catalyst was filtered off and the filtrate concentrated *in vacuo* to give the free α-amino dipeptide (414 mg, 2.71 mmol). ^{1}H NMR (300 MHz, CD_3OD, δ): 1.29 (d, *J* = 6.9 Hz, 3H), 1.39 (d, *J* = 6.9 Hz, 3H), 3.44 (q, *J* = 6.9 Hz, 1H), 4.35 (q, *J* = 6.7 Hz, 1H). MS *m/z* 160 $[M + H]^+$, 182 $[M + Na]^+$.



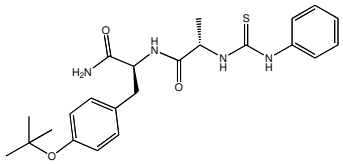
***t*-Butyl(S)-5-amino-4-((R)-2-aminopropanamido)-5-oxopentylcarbamate** was prepared by **General method F** on a 1.82 mmol scale via the free amine that was taken on to the protected dipeptide (545.2 mg, 1.25 mmol) ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.42 (d, *J* = 7.1Hz, 3H), 1.45 (s, 9H), 1.50-1.58 (m, 3H), 1.83-1.99 (m, 1H), 3.01-3.22 (m, 1H), 3.27-3.51 (m,

1H), 4.19-4.37 (m, 1H), 4.52-4.71 (m, 1H), 4.77 (br s, 1H), 5.12 (d, *J* = 2.4 Hz, 2H), 5.39 (br s, 2H), 6.76 (br s, 1H), 7.05 (br s, 1H), 7.32-7.50 (m, 5H).; MS *m/z* 437 $[M + H]^+$, 459 $[M + Na]^+$. This was carried on to the α amino δ-Boc dipeptide amide (281.3 mg, 0.93 mmol). ^{1}H NMR (300 MHz, CD_3OD, δ): 1.29 (d, *J* = 6.9 Hz, 3H), 1.45 (s, 9H), 1.49-1.76 (m, 3H), 1.78-1.95 (m, 1H), 3.08 (t, *J* = 6.2 Hz, 2H), 3.48 (q, *J* = 7.0 Hz, 1H), 4.29-4.44 (m, 1H). MS *m/z* 303 $[M + H]^+$, 325.2 $[M + Na]^+$.

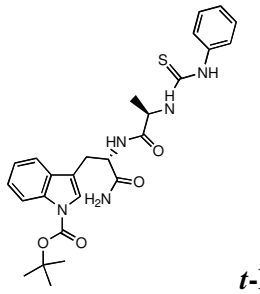


***t*-Butyl(S)-4-amino-5-((S)-1-amino-1-oxopropan-2-ylamino)-5-oxopentylcarbamate** was prepared by **General method F** on a 1.85 mmol scale via alaninamide to the protected dipeptide (222.5 mg, 0.51 mmol) ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.41 (d, *J* = 6.87 Hz, 3H), 1.46 (s, 9H), 1.64-2.02 (m, 4H), 3.01-3.20 (m, 1H), 3.26-3.47 (m, 1H), 4.47 (t, *J* = 7.1 Hz, 1H), 4.66-4.81 (m, 1H), 5.13 (s, 2H), 5.27 (br s, 1H), 5.59 (br s, 1H), 6.26 (br s, 1H), 6.87 (br s, 1H), 7.32-7.66 (m, 5H); MS *m/z* 459 $[M + Na]^+$; to the α-amino dipeptide amide (122.4 mg, 0.41 mmol). ^{1}H NMR (300 MHz, CD_3OD, δ): 1.39 (d, *J* = 7.2 Hz, 3H), 1.44 (s, 9H), 1.50-1.63 (m, 3H), 1.63-1.80 (m, 1H), 3.06 (t, *J* = 6.5 Hz, 2H), 3.25-3.54 (br, solvent envelope over CH), 4.38 (q, *J* = 7.2 Hz, 1H). MS *m/z* 303 $[M + H]^+$, 325 $[M + Na]^+$.

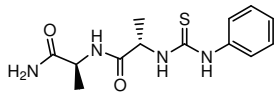
General method G



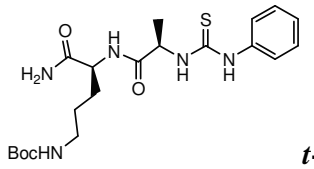
(*S*)-*N*-((*S*)-1-Amino-3-(4-*tert*-butoxyphenyl)-1-oxopropan-2-yl)-2-(3-phenylthioureido)propanamide was prepared by **General method G** to give 90 mg, 0.20 mmol that was used without further purification. ^{1}H NMR (300 MHz, $(CD_3)_2CO$, δ): 1.39 (s, 9H), 1.43 (d, *J* = 7.1 Hz, 3H), 2.07 (br, 1H), 2.91 (dd, *J* = 9.2, 4.7 Hz, 1H), 3.19 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.61-4.63 (m, 1H), 4.86-4.87 (m, 1H), 6.83 (br, 1H), 6.87-6.89 (m, 2H), 7.15-7.69 (m, 7H), 9.42 (br, 2H). ^{13}C NMR (500 MHz, $(CD_3)_2CO$, δ): 21.60, 32.24, 40.71, 57.83, 58.30,81.67,127.56, 127.83, 128.89, 132.80, 133.81, 16.53, 158.07, 176.53, 177.64, 184.95. MS *m/z* 352 $[M - PhNH + H]^+$, 443 $[M + H]^+$, 465 $[M + Na]^+$, 481 $[M + K]^+$.



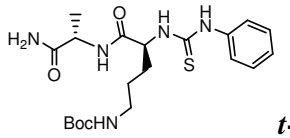
***t*-Butyl 3-((*S*)-3-amino-3-oxo-2-((*S*)-2-(3-phenylthioureido)propanamido)propyl)-1*H*-indole-1-carboxylate** was prepared by **General method G** on a 0.19 mmol scale to give, after silica gel purification using a gradient of 0 to 10% MeOH in $CHCl_3$ (67 mg, 0.13 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $(CD_3)_2CO$), δ): 1.26 (d, *J* = 7.0 Hz, 3H), 1.65 (s, 9H), 3.12 (dd, *J* = 8.3, 6.5 Hz, 1H), 3.34 (dd, *J* = 9.3, 5.4 Hz, 1H), 4.78-4.79 (m, 1H), 4.79 (m, 1H), 6.6-6.7 (br, 1H), 7.16-8.14 (m, 10H), 9.14 (br, 1H). MS *m/z* 510 $[M + H]^+$, 532 $[M + Na]^+$.



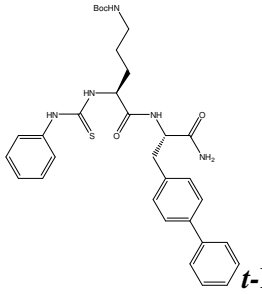
(S)-N-((S)-1-Amino-1-oxopropan-2-yl)-2-(3-phenylthioureido)propanamide was prepared by **General method G** on a 1.86 mmol scale to yield 448.9 mg (1.53 mmol) product. ^{1}H NMR (300 MHz, CD_3OD, δ): 1.38 (d, *J* = 6.90 Hz, 3H), 1.43 (d, *J* = 6.9 Hz, 3H), 3.34-3.44 (m, 1H), 4.27-4.47 (m, 1H), 7.12-7.56 (m, 5H). ^{13}C NMR (500 MHz, CD_3OD, δ): 20.81, 21.19, 53.05, 58.17, 128.56, 129.99, 133.51, 134.29, 178.78, 181.27, 186.08. MS *m/z* 317 $[M + Na]^+$.



***t*-Butyl(S)-5-amino-5-oxo-4-((R)-2-(3-phenylthioureido)propanamido)pentylcarbamate** was prepared by **General method G** on a 0.93 mmol scale, but allowed to react for 2 days to go to completion to give 274 mg (0.63 mmol) product. ^{1}H NMR (300 MHz, CD_3OD, δ): 1.45 (s, 9H), 1.45 (d, *J* = 6.9 Hz, 3H), 1.51-1.80 (m, 3H), 1.85-2.20 (m, 1H), 3.08 (t, *J* = 6.6 Hz, 2H), 4.26-4.40 (m, 1H), 4.94 (q, *J* = 7.1 Hz, 1H), 7.14-7.25 (m, 1H), 7.32-7.58 (m, 4H). MS *m/z* 438 $[M + H]^+$, 460 $[M + Na]^+$.

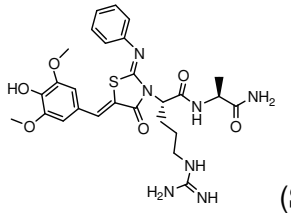


***t*-Butyl(S)-5-((S)-1-amino-1-oxopropan-2-ylamino)-5-oxo-4-(3-phenylthioureido)pentylcarbamate** was prepared by **General method G** on a 0.40 mmol scale to yield 164.5 mg (0.38 mmol) product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.46 (s, 9H), 1.48-1.83 (m, 6H), 1.86-2.04 (m, 1H), 3.04-3.20 (m, 1H), 3.33-3.62 (m, 1H), 4.39-4.57 (m, 1H), 4.80 (br s, 1H), 5.03-5.28 (m, 1H), 5.32 (br s, 1H), 6.31 (br s, 1H), 6.93 (br s, 1H), 7.12 (br s, 1H), 7.30-7.42 (m, 3H), 7.47 (t, *J* = 7.3 Hz, 2H). MS *m/z* 438.4 $[M + H]^+$, 460 $[M + Na]^+$.



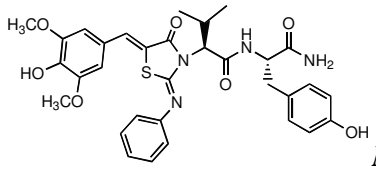
***t*-Butyl(S)-5-((S)-1-amino-3-(biphenyl-4-yl)-1-oxopropan-2-ylamino)-5-oxo-4-(3-phenylthioureido)pentylcarbamate** Crude protected OrnBip dipeptide amide was reacted with phenylisothiocyanate by **General method G** to yield, after silica gel purification using a gradient from 1 to 10% MeOH in CH_2Cl_2, 48 mg (0.08 mmol) product. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 1.48 (s, 9H), 1.64-1.80 (m, 2H), 1.80-1.98 (m, 2H), 2.74-3.36 (m, 4H), 4.58-4.82 (m, 1H), 4.91 (br s, 1H), 5.03-5.34 (m, 1H), 5.92 (br s, 1H), 6.63 (br s, 1H), 7.03-7.72 (m, 14H), 8.37 (br s, 1H). MS *m/z* 590 $[M + H]^+$, 612.3 $[M + Na]^+$.

General method H



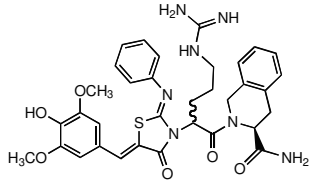
(S)-N-((S)-1-Amino-1-oxopropan-2-yl)-5-guanidino-2-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)pentanamide 46 was prepared by **General method H** via the ornithine **45** (22 mg, 0.04 mmol) to give the *bis*-Boc-guanidine intermediate that was converted directly to the free guanidine, purified on reverse phase HPLC (10 to 75 % B in A over 30 min) to give **46** (7.1 mg, 0.01 mmol) as the TFA salt. ^{1}H NMR (500 MHz, CD_3OD, δ): 1.35 (d, *J* = 7.2 Hz, 3H), 1.55-1.81 (m, 2H), 2.20-2.50 (m, 2H), 3.12-3.32 (m, 2H), 3.84 (s, 6H), 4.34-4.55 (m, 1H), 5.38 (t, *J* = 7.5 Hz, 1H), 6.82 (s, 2H), 7.05 (d, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.74 (s, 1H). ^{13}C NMR (500 MHz, CD_3OD, δ): 20.70, 28.81, 29.40, 44.62, 53.20, 59.47, 60.22, 111.70, 121.45, 124.80, 128.37, 128.86, 133.07, 136.17, 142.44, 151.71, 152.24, 153.67, 161.24, 170.88, 173.25, 180.33. MS *m/z* 584 $[M + H]^+$. HRMS (*m/z*): calcd for $C_{27}H_{34}N_7O_6S$, 584.2286; found 584.2288.

Scheme 3



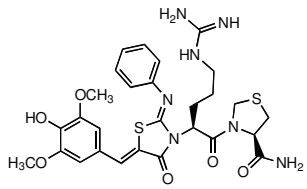
***N*-((*S*)-1-Amino-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)-2-((2*Z*,5*Z*)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)-3-methylbutanamide 42**

^{1}H NMR (500 MHz, CD_3CN, δ): 0.48 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 7.1 Hz, 3H), 2.0-2.10 (m, 1H), 2.90-3.10 (m, 2H), 3.61 (s, 6H), 3.73 (d, *J* = 4.2 Hz, 1H), 4.30-4.39 (m, 1H), 5.8 (br, 1H), 6.3 (br, 1H), 6.58 (d, *J* = 10.5 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 6.92 (s, 2H), 7.43-7.62 (m, 5H), 7.69 (s, 1H). MS *m/z* 619 $[M + H]^+$, 641 $[M + Na]^+$. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{32}H_{35}N_4O_7S$, 619.2221; found 619.2216; $[M + Na]^+$ calcd for $C_{32}H_{34}N_4NaO_7S$, 641.2040; found 641.2033.



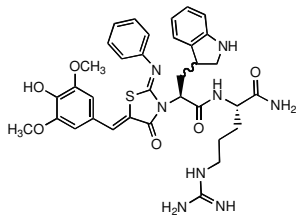
(*S*)-2-(5-Guanidino-2-((2*Z*,5*Z*)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)pentanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide 47

^{1}H NMR (500 MHz, CD_3CN, δ): 1.40-1.80 (m, 2H), 1.85-2.00 (m, 1H), 2.00-2.50 (m, 1H), 2.80-3.40 (m, 2H), 3.40-3.95 (m) over 3.66 (s, 8H total), 4.20-4.45 (m, 1H), 4.60-4.80 (m, 2H), 6.40-7.80 (m, 12H). MS *m/z* 672 $[M + H]^+$. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{34}H_{38}N_7O_6S$, 672.2599; found 672.2590.



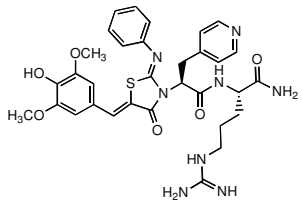
(*R*)-3-(5-Guanidino-2-((2*Z*,5*Z*)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)pentanoyl)thiazolidine-4-carboxamide 48

^{1}H NMR (500 MHz, CD_3CN, δ): 1.71-1.85 (m, 2H), 1.96-1.97 (m, 2H), 2.76-2.77 (m, 1H), 3.22 (br, 1H), 3.30-3.31 (m, 1H), 3.62 (s, 3H), 3.83 (s, 2H), 3. 94 (s, 1H), 4.47-4.54 (m, 1H), 4.61-4.66 (m, 1H), 4.83-4.90 (m, 1H), 4.96-5.09 (m, 1H), 5.44-5.58 (m, 2H), 5.91-6.02 (m, 1H), 6.82 (s, 1H), 6.92 (s, 1H), 7.09-7.58 (m, 5H), 7.69 (s, 1H). MS *m/z* 628 $[M + H]^+$. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{28}H_{34}N_7O_6S_2$, 628.2006; found 628.2018.



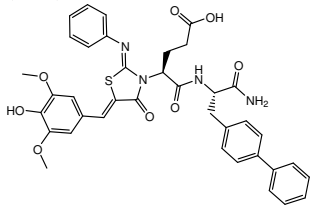
(2*S*)-5-Guanidino-2-((2*S*)-2-((2*Z*,5*Z*)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)-3-(indolin-3-yl)propanamido)pentanamide 50

^{1}H NMR (500 MHz, CD_3CN, δ): 1.60-1.85 (m, 2H), 2.54-2.94 (m, 3H), 3.09-3.16 (m, 3H), 3.50-3.68 (m, 3H), 3.84 (s, 6H), 4.38-4.47 (m, 1H), 5.47-5.60 (m, 1H), 5.82 (br, 1H), 6.83 (s, 2H) over 6.70-7.44 (m, 9H), 7.72 (s, 1H), 7.91 (br, 1H). MS *m/z* 702 $[M + H]^+$. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{35}H_{41}N_8O_6S$, 701.2864; found 701.2875

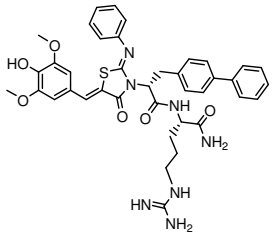


(*S*)-5-Guanidino-2-(2-((2*Z*,5*Z*)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)-3-(pyridin-4-yl)propanamido)pentanamide 51

^{1}H NMR (500 MHz, CD_3CN, δ): 1.61-1.75 (m, 2H), 2.76-2.77 (m, 1H), 3.55-3.72 (m, 2H), 3.82 (s, 2H), 3.92 (s, 1H), 4.33-4.52 (m, 1H), 5.65-5.67 (m, 1H), 5.82 (br, 1H), 6.77 (s, 2H), 6.80-7.69 (m, 10H), 7.73 (s, 1H), 8.22-8.46 (br, 1H), 8.47-8.51 (br, 2H). MS *m/z* 661 $[M + H]^+$. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{32}H_{37}N_8O_6S$, 661.2551; found 661.2576.



(S)-5-((S)-1-Amino-3-(biphenyl-4-yl)-1-oxopropan-2-ylamino)-4-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)-5-oxopentanoic acid 53 ^{1}H NMR (500 MHz, CD_3OD, δ): 2.36-2.50 (m, 2H), 2.50-2.71 (m, 2H), 3.02-3.15 (m, 1H), 3.21-3.29 (m, 1H), 3.71 (s, 6H), 4.63-4.74 (m, 1H), 5.33-5.45 (m, 1H), 6.65 (s, 2H), 6.91 (d, *J* = 7.9 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.23-7.38 (m, 9H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.62 (s, 1H). MS *m/z* 709 $[M + H]^+$. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{38}H_{37}N_4O_8S$, 709.2327; found 709.2328.



(S)-2-((R)-3-(Biphenyl-4-yl)-2-((2Z,5Z)-5-(4-hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)propanamido)-5-guanidinopentanamide 55b

^{1}H NMR (500 MHz, CD_3OD, δ): 1.64-1.86 (m, 3H), 2.01-2.15 (m, 1H), 3.13-3.30 (m, 2H), 3.53-3.72 (m, 2H), 3.79 (s, 6H), 4.51-4.62 (m, 1H), 5.67-5.78 (m, 1H), 6.73 (s, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.24-7.37 (m, 5H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.50-7.62 (m, 4H), 7.66 (s, 1H). MS *m/z* 737 $[M + H]^+$. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{39}H_{42}N_7O_6S$, 736.2912; found 736.2918.

HPLC data:

A 4.6 x 250 mm Alltech C18 5mM reverse phase column was used for all analytical work, run on a Varian HPLC instrument.

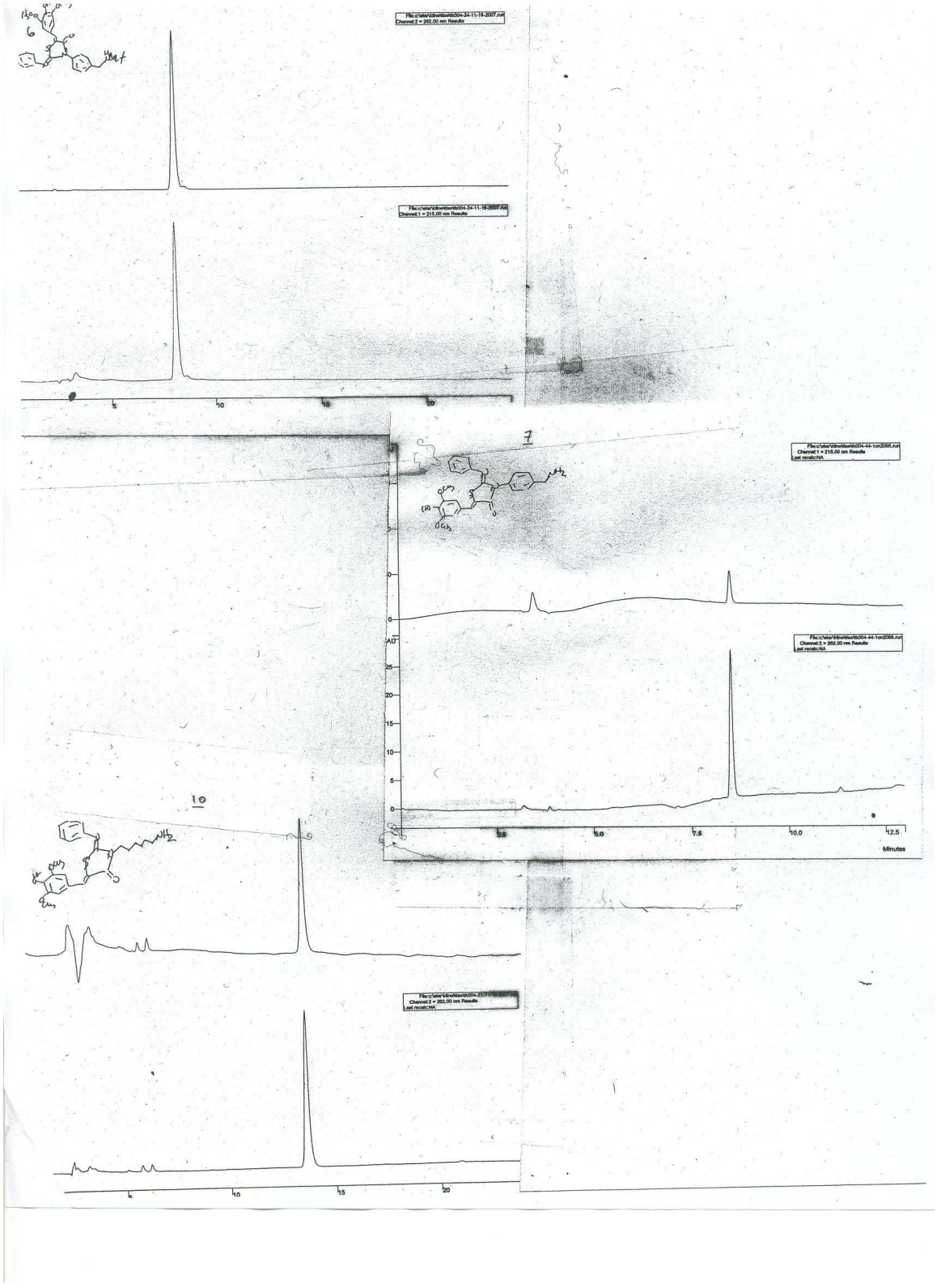
All methods refer to a linear gradient of buffer B (0.05% TFA in CH_3CN) in buffer A (0.05% TFA in H_2O) at 1 mL/min over the time period stated. Peaks were monitored at the stated wavelength(s).

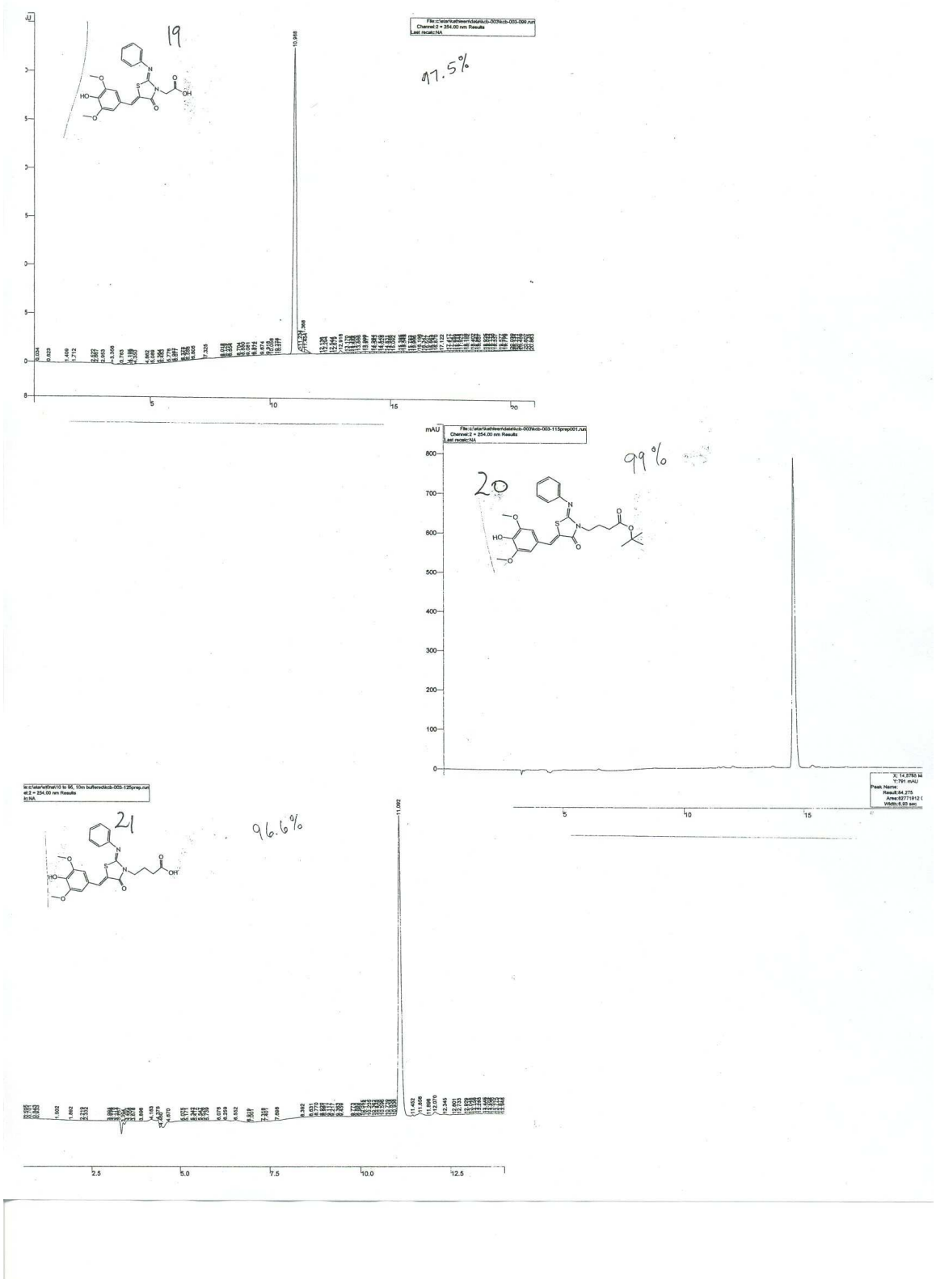
Methods:

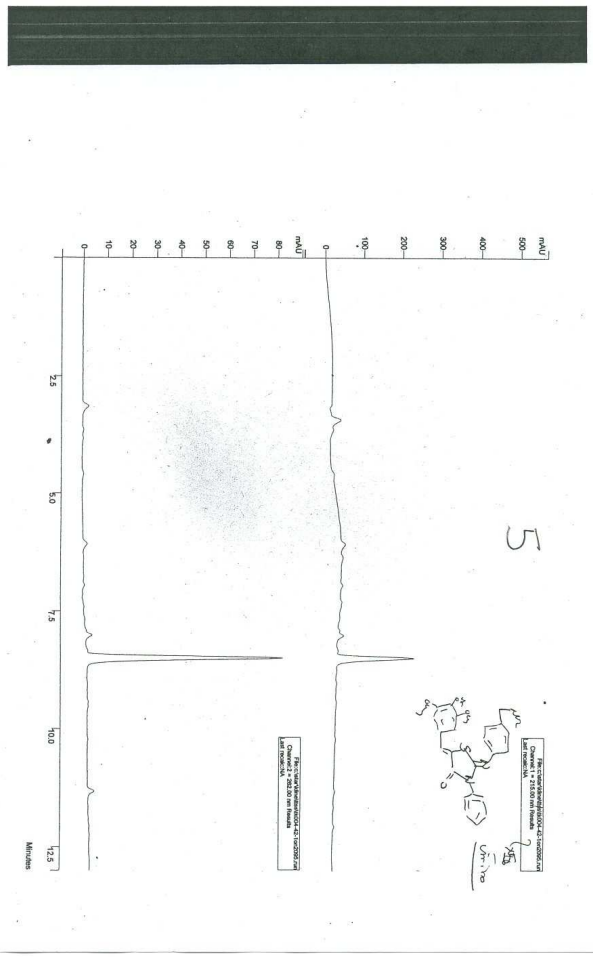
A 10 to 95% in 10 minutes, 254 nM
B 20 to 95% in 10 minutes, 215, 262 nM
C 20 to 95% in 15 minutes, 215, 262 nM
D 20 to 95% in 10 minutes, 215, 360 nM
E 65 to 85% in 12 minutes, 215, 360 nM
F 10 to 85% in 5minutes, 85 to 95% in10 minutes, 215, 254 nm
G 50 to 60% in 15 minutes, 215, 254 nM
H 10 to 95% in 10 minutes, iso 95% 10 minutes, 215, 254 nM
I 70 to 95% in 14 minutes, 215, 254 nM
J 50 to 60% in 15 minutes, 215, 254 nM
K 60 to 80% in 15 minutes, 215, 254 nM
L 10 to 60% in 20 minutes, 215, 254 nM

compound number	retention time (minutes)	purity (%)	method
7	8.1	99	E
8	8.5	95	D
12	9.3	95	D
23	11.0	98	A
24	14.6	99	A
25	11.1	97	A
26	16.2	96	J
27	17.3	90	H
28	17.8	94	I
31	15.9	94	I
36	20.1	96	I
33	18.7	93	I
34	20.0	91	I
29	13.8	93	J
30	11.4	92	H
6	8.5	90	D
36	19.6	98	I
35	13.9	95	J
37	16.2	96	J
38	15.6	97	I
39	12.9, 13.5	98	K
40	18.5, 18.7	96	I
41	10.3	97	A
42	13.7	96	C
43	11.9	99	C
44a	12.6, 13.6	38, 62	C

44b	13.6	80	C
20a	8.6	95	A
20b	8.8	97	A
22a	8.9	96	A
22b	9.0	99	A
45	8.2	91	A
46	8.5	95	A
47	8.5	93	C
48	8.7	93	B
49a	13.9	95	L
49b	14.1	95	L
50	7.0	83	B
51	6.5	90	B
52	9.7	98	A
53	11.0	95	A
54	11.6	95	C
55a	10.2	97	B
55b	11.0	96	A
56	10.0	96	B


6
7
10
Minutes


19
97.5%
20
99%
21
96.6%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20
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40
50
60
70
80
mAU
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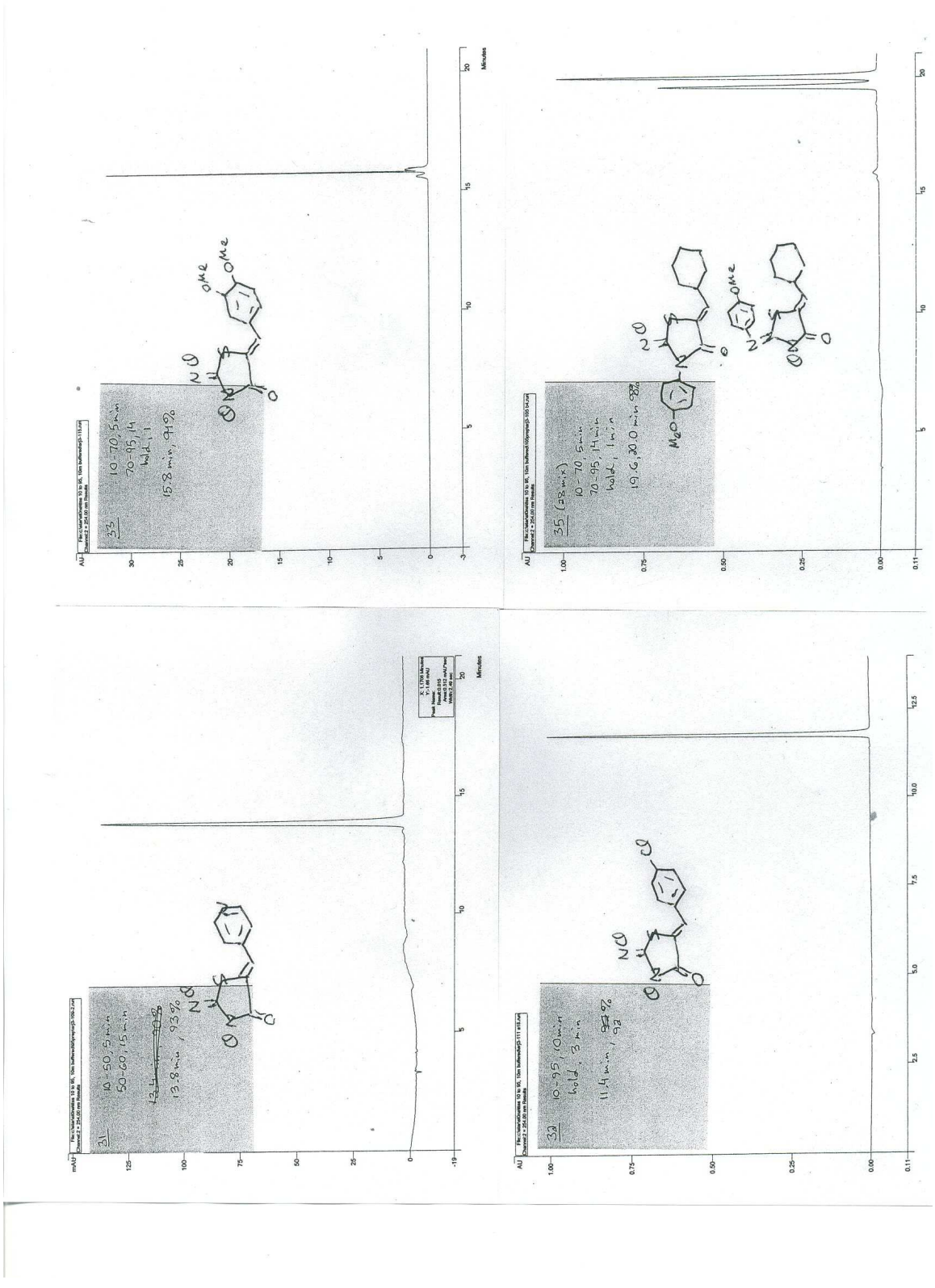
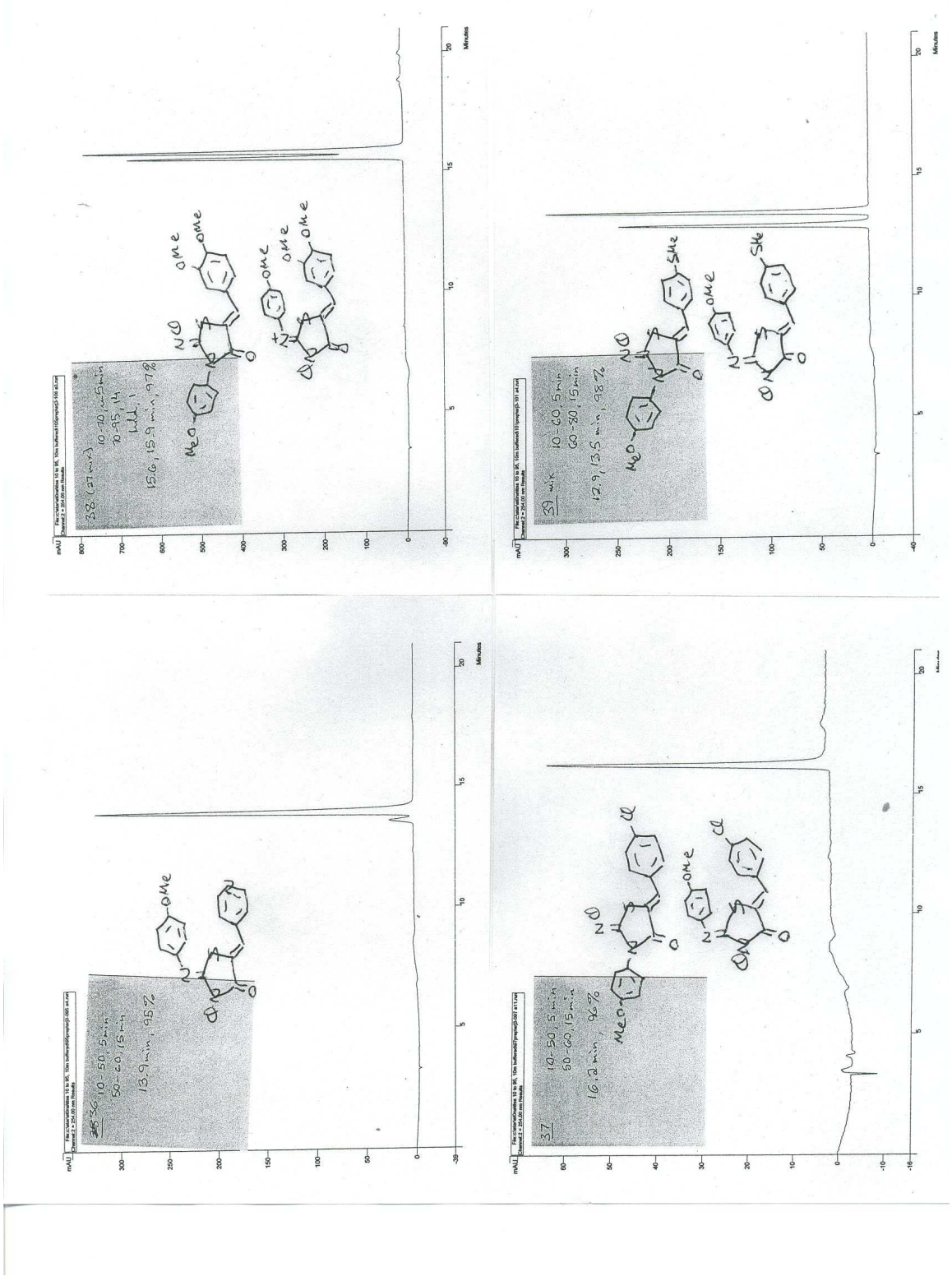
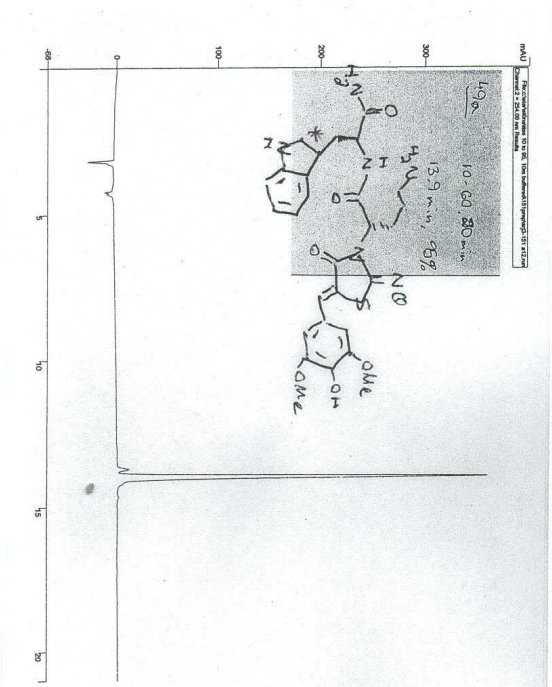
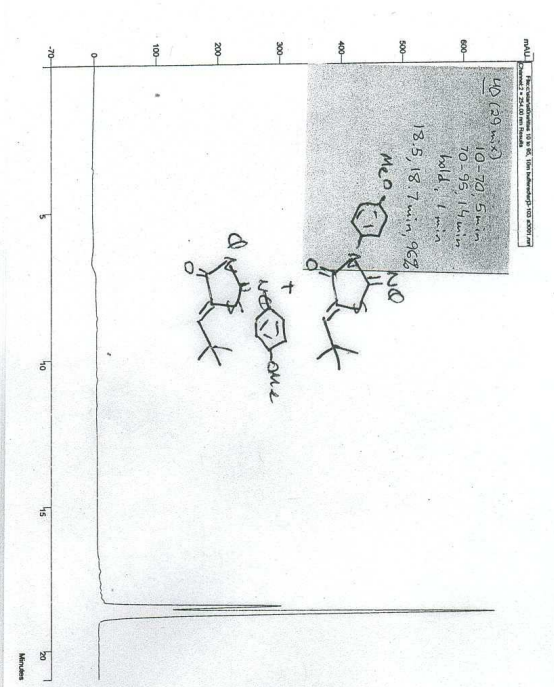
100
200
300
400
500
2.5
5.0
7.5
10.0
12.5
Minutes

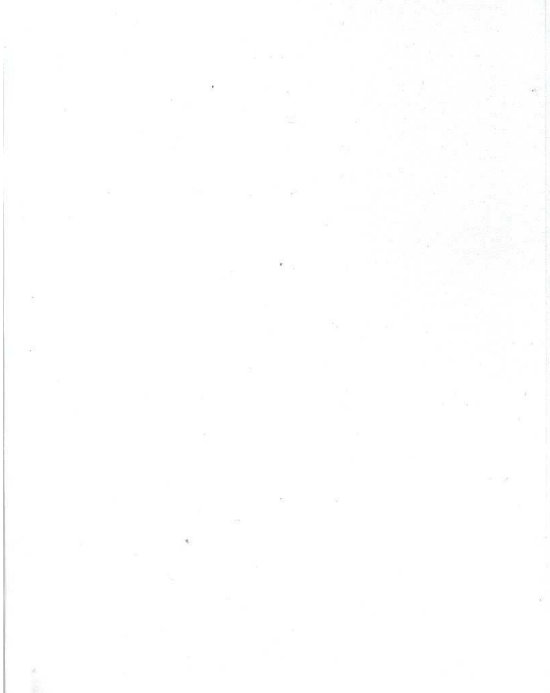

29
10-70, 5 min
70-95, 14
MeOH, 1
18.7 min, 93%
30
10-70, 5 min
70-95, 14 min
MeOH, 1
20.0 min, 91%
27
10-70, 5 min
70-95, 14
MeOH, 1
15.9 min, 94%
28
10-70, 5 min
70-95, 14 min
MeOH, 1 min
20.1 min, 96%
Minutes

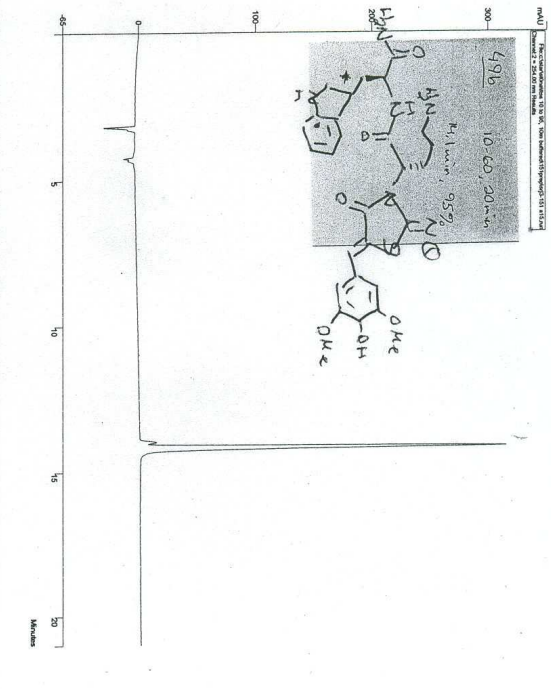


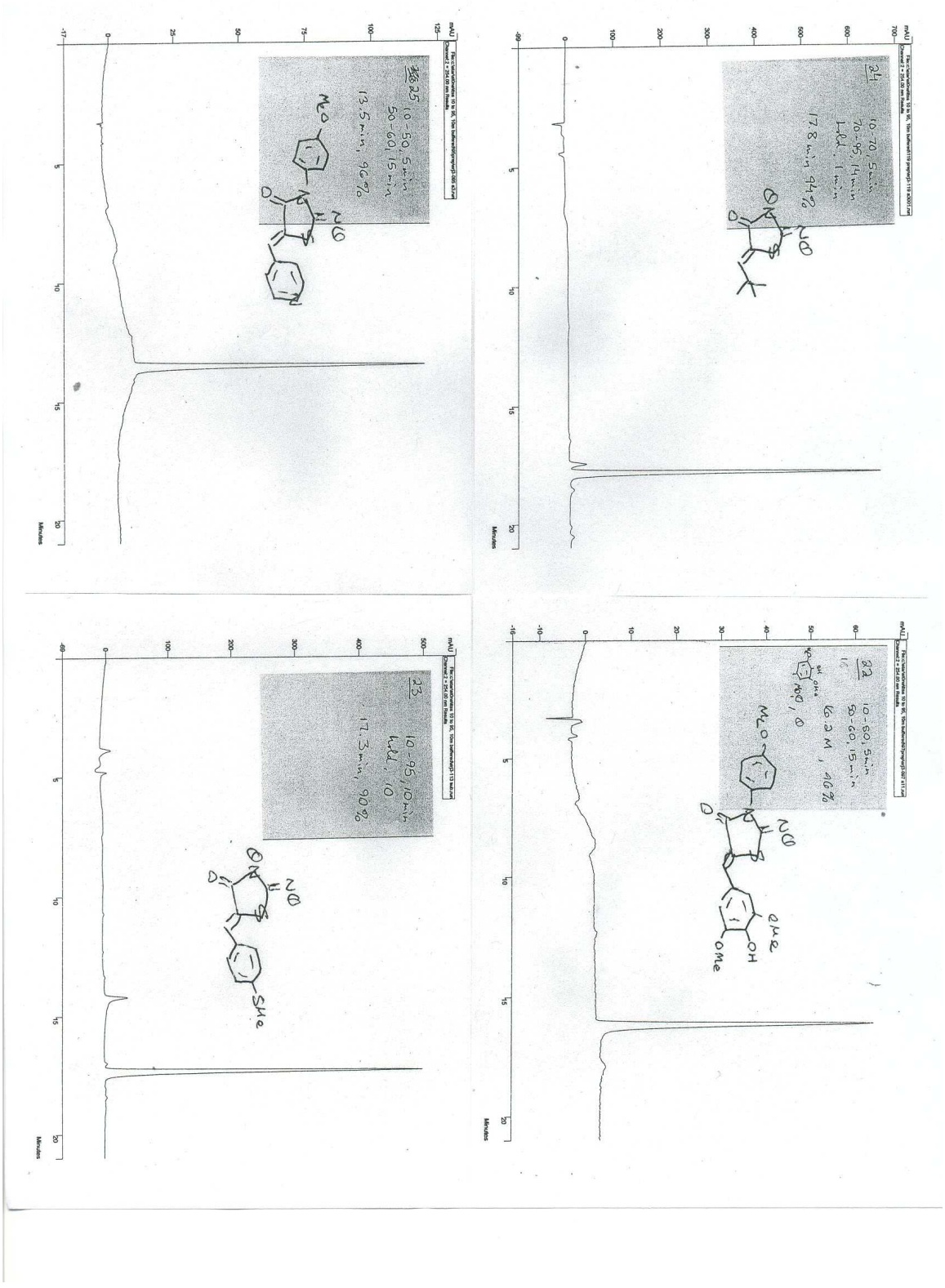








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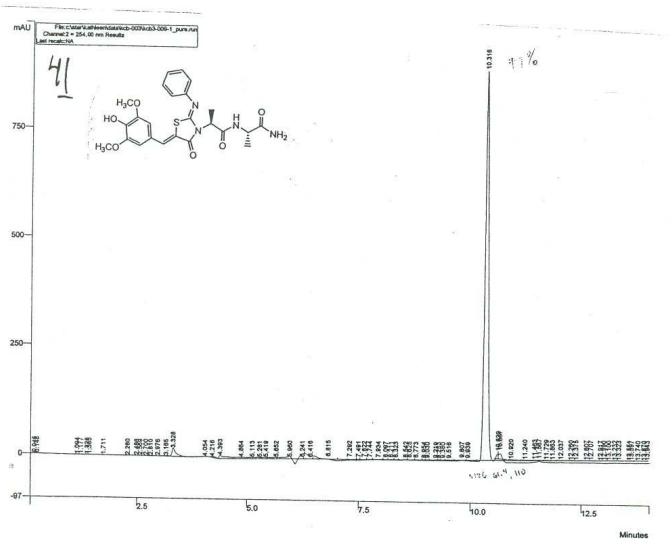
10-70, 5 min
70-95, 14 min
1.82, 1 min
17.8 min, 94%
22
10-60, 5 min
50-60, 15 min
6.3 M, 10%
23
10-95, 10 min
tR = 17.3 min, 90%
25
10-50, 5 min
50-60, 15 min
13.5 min, 96%
Minutes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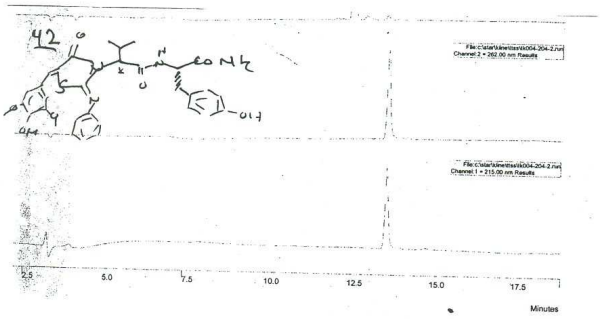
500
250
0
-97
10.318
2.5
5.0
7.5
10.0
12.5
Minutes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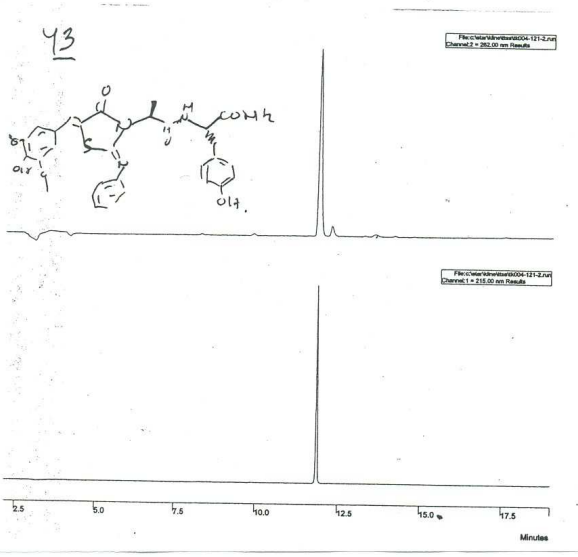
2.5
5.0
7.5
10.0
12.5
15.0
17.5
Minutes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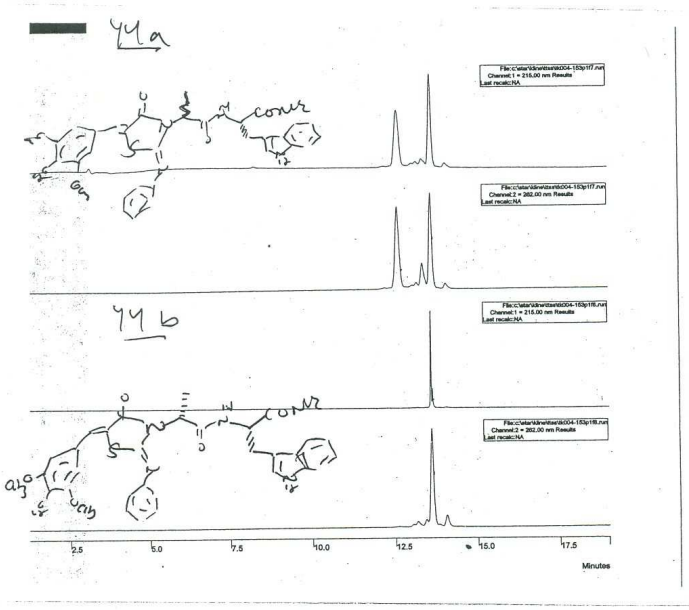
5.0
7.5
10.0
12.5
15.0
17.5
Minutes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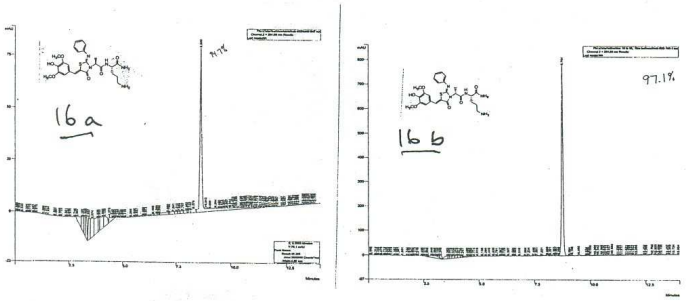
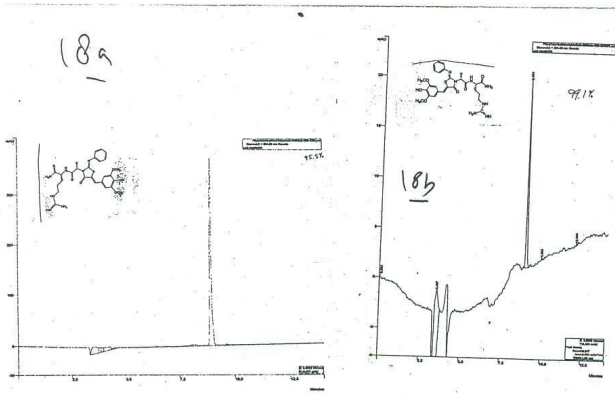
44b
2.5
5.0
7.5
10.0
12.5
15.0
17.5
Minutes


16a
16b
97.1%


18a
18b
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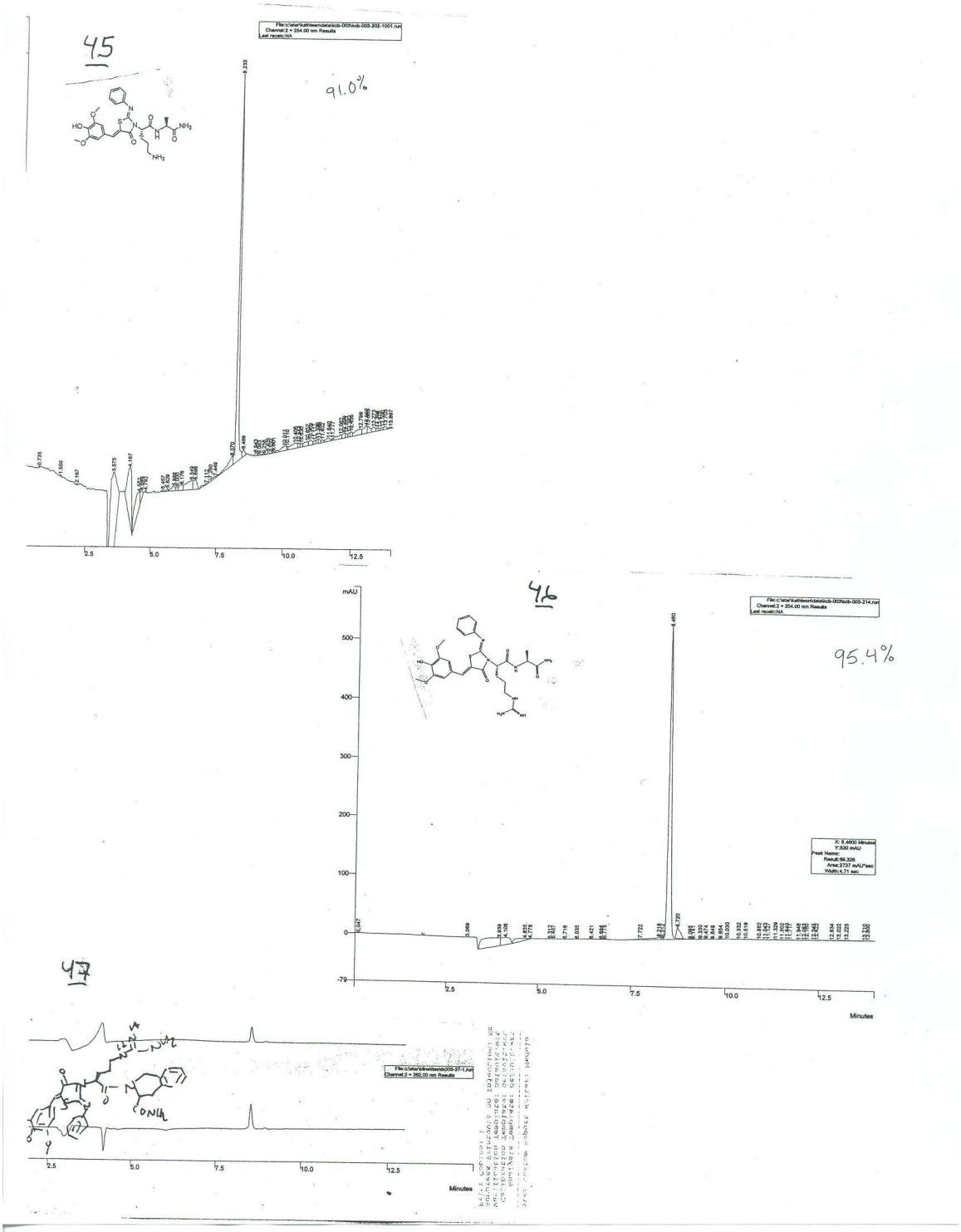
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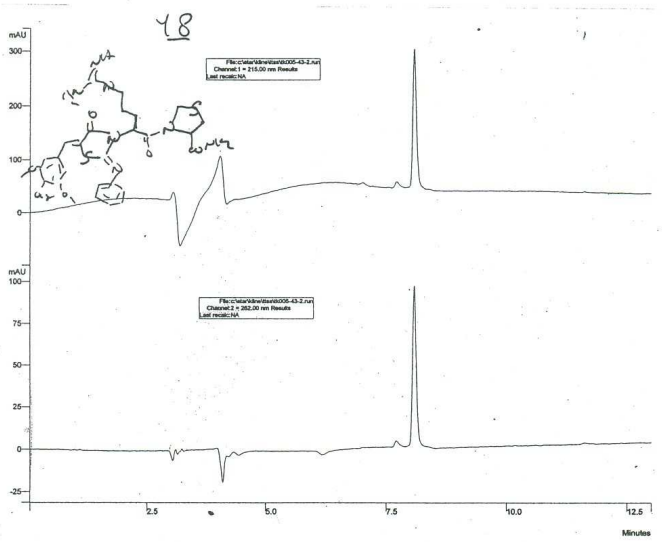
46
95.4%
47
Minutes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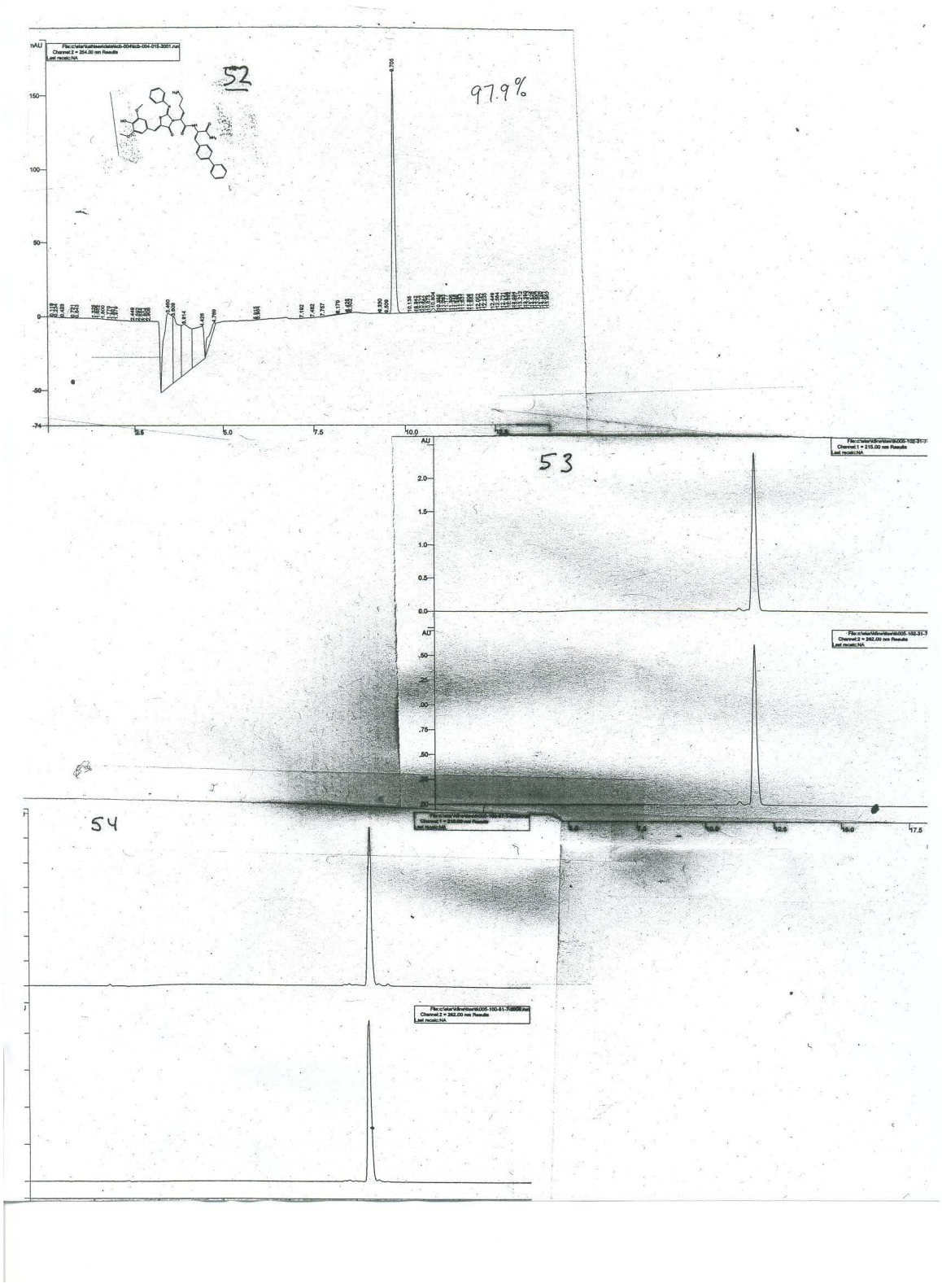
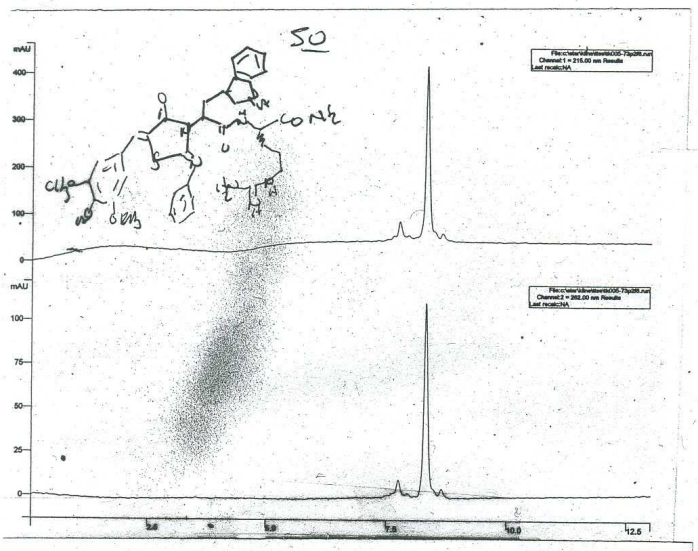
10.0
12.5
Minutes


52
97.9%
53
54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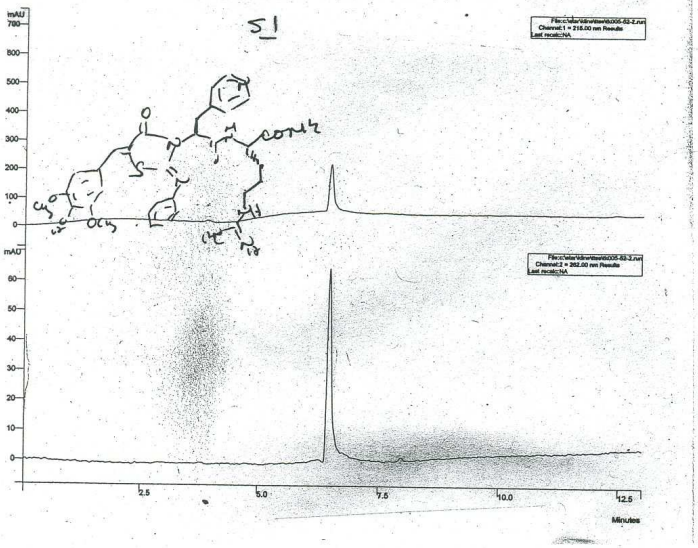
51
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mAU
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Minutes