

Supplemental Information

Discovery of Dual inducible/neuronal Nitric Oxide Synthase (iNOS/nNOS) inhibitor Development Candidate KD7332 (Part 2): Identification of a Novel, Potent and Selective series of Benzimidazole-Quinolinone iNOS/nNOS Dimerization Inhibitors that are Orally Active in Pain Models

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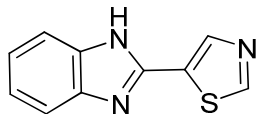
Ludwig Cancer Research Center, University of California, San Diego, CA92037 (AKS)

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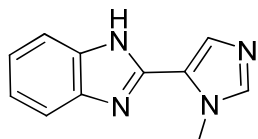
Experimental procedure for the preparation of intermediates 79-119.

5-(1*H*-Benzo[*d*]imidazol-2-yl)thiazole (79)



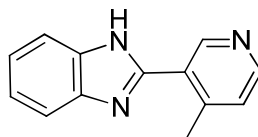
Compound **79** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and thiazole-5-carboxylic acid (**61**) as the starting materials (60% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.14 (s, 1H), 9.21 (s, 1H), 8.56 (s, 1H), 7.57 (m, 2H), 7.20 (m, 2H). LRMS (ESI+) *m/z*: calcd for C₁₀H₇N₃S 202.0, found 201.9 [M + H]⁺.

2-(1-Methyl-1*H*-imidazol-5-yl)-1*H*-benzo[*d*]imidazole (80)



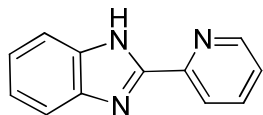
Compound **80** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and 1-methyl-1*H*-imidazole-5-carboxylic acid (**62**) as the starting materials (65% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.68 (s, 1H), 7.85 (s, 1H), 7.68 (s, 1H), 7.64 (d, 1H, *J* = 7.2 Hz), 7.48 (d, 1H, *J* = 7.2 Hz), 7.19 (m, 2H), 4.07 (s, 3H). LRMS (ESI+) *m/z*: calcd for C₁₁H₁₀N₄ 199.1, found 198.9 [M + H]⁺.

2-(4-Methylpyridin-3-yl)-1*H*-benzo[*d*]imidazole (81)



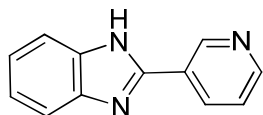
Compound **81** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and 4-methylnicotinic acid (**63**) as the starting materials (65% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.84 (s, 1H), 8.91 (s, 1H), 8.53 (d, 1H, *J* = 4.8 Hz), 7.71 (m, 1H), 7.57 (m, 1H), 7.42 (d, 1H, *J* = 5.2 Hz), 7.25 (m, 2H), 2.65 (s, 3H). LRMS (ESI+) *m/z*: calcd for C₁₃H₁₁N₃ 210.1, found 209.9 [M + H]⁺.

2-(Pyridin-2-yl)-1H-benzo[d]imidazole (82)



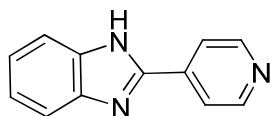
Compound **82** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and picolinic acid (**64**) as the starting materials (58% yield). ^1H NMR (400 MHz, DMSO- d_6) δ NH resonance not observed, 8.77 (d, 1H, $J = 4.4$ Hz), 8.37 (d, 1H, $J = 7.6$ Hz), 8.06 (td, 1H, $J = 8.0, 1.6$ Hz), 7.69 (m, 2H), 7.58 (ddd, 1H, $J = 7.6, 4.4, 0.8$ Hz), 7.32 (m, 2H). LRMS (ESI+) m/z : calcd for $\text{C}_{12}\text{H}_9\text{N}_3$ 196.1, found 196.0 $[\text{M} + \text{H}]^+$.

2-(Pyridin-3-yl)-1H-benzo[d]imidazole (83)



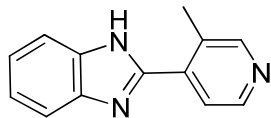
Compound **83** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and nicotinic acid (**65**) as the starting materials (83% yield). ^1H NMR (400 MHz, DMSO- d_6) δ NH resonance not observed, 9.35 (s, 1H), 8.69 (d, 1H, $J = 4.8$ Hz), 8.52 (d, 1H, $J = 8.0$ Hz), 7.67-7.60 (m, 3H), 7.26 (m, 2H). LRMS (ESI+) m/z : calcd for $\text{C}_{12}\text{H}_9\text{N}_3$ 196.1, found 196.8 $[\text{M} + \text{H}]^+$.

2-(Pyridin-4-yl)-1H-benzo[d]imidazole (84)



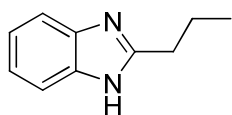
Compound **84** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and isonicotinic acid (**66**) as the starting materials (42% yield). ^1H NMR (400 MHz, DMSO- d_6) δ 13.24 (s, 1H), 8.74 (d, 2H, $J = 4.8$ Hz), 8.08 (d, 2H, $J = 4.6$ Hz), 7.71 (m, 1H), 7.59 (m, 1H), 7.25 (m, 2H).

2-(3-Methylpyridin-4-yl)-1H-benzo[d]imidazole (85)



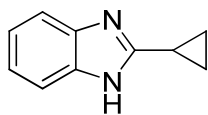
Compound **85** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and 3-methylisonicotinic acid (**67**) as the starting materials (21% yield). ^1H NMR (400 MHz, DMSO- d_6) δ 12.95 (s, 1H), 8.62 (s, 1H), 8.58 (d, 1H, $J = 5.2$ Hz), 7.78 (d, 1H, $J = 5.2$ Hz), 7.73 (m, 1H), 7.59 (m, 1H), 7.26 (m, 2H), 2.67 (s, 3H).

2-Propyl-1H-benzo[d]imidazole (**86**)



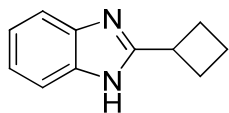
Compound **86** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and butyric acid (**68**) as the starting materials (74% yield). ^1H NMR (400 MHz, DMSO- d_6) δ 12.08 (s, 1H), 7.43 (m, 2H), 7.08 (m, 2H), 2.75 (t, 2H, $J = 7.4$ Hz), 1.76 (m, 2H), 0.92 (t, 3H, $J = 7.4$ Hz).

2-Cyclopropyl-1H-benzo[d]imidazole (**87**)



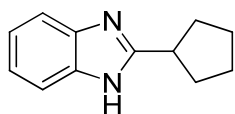
A mixture of benzene-1,2-diamine (**59**, 1 g, 9.3 mmol) and cyclopropanecarboxylic acid (**69**) (5.8 mL, 74.1 mmol) in aqueous HCl (3M, 10 mL) was heated to 100°C for 18 h. The reaction mixture was cooled to 25°C and poured into an ice/H₂O slurry. NaOH (1M, about 30 mL) was added until a fine precipitate formed. The aqueous layer was extracted with DCM (5 x 50 mL). The organics were combined, dried over Na₂SO₄, and dried under reduced pressure. The crude was purified by silica gel chromatography (50% to 100% EtOAc/Hexanes) to afford 1.2 g (82%) of 2-cyclopropyl-1H-benzo[d]imidazole (**87**) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 12.10 (s, 1H), 7.44 (d, 1H, $J = 5.6$ Hz), 7.35 (d, 1H, $J = 6.4$ Hz), 7.07 (m, 2H), 2.09 (m, 1H), 1.06-0.99 (m, 4H).

2-Cyclobutyl-1H-benzo[d]imidazole (**88**)



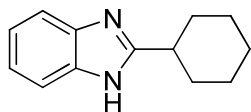
Compound **88** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and cyclobutanecarboxylic acid (**70**) as the starting materials (heated to 190°C) (81% yield). ^1H NMR (400 MHz, DMSO- d_6) δ 12.16 (s, 1H), 7.46 (m, 2H), 7.11 (m, 2H), 3.69 (qt, 1H, $J = 8.8$ Hz), 2.44-2.26 (m, 4H), 2.05 (m, 1H), 1.92 (m, 1H).

2-Cyclopentyl-1H-benzo[d]imidazole (**89**)



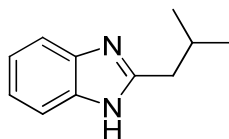
Compound **89** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and cyclopentanecarboxylic acid (**71**) as the starting materials (heated to 190°C) (61% yield). ^1H NMR (400 MHz, DMSO- d_6) δ NH resonance not observed, 7.45 (m, 2H), 7.09 (m, 2H), 3.26 (qt, 1H, $J = 8.2$ Hz), 2.09-2.01 (m, 2H), 1.93-1.84 (m, 2H), 1.79-1.71 (m, 2H), 1.69-1.62 (m, 2H).

2-Cyclohexyl-1H-benzo[d]imidazole (**90**)



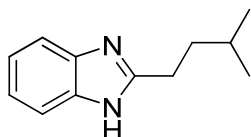
Compound **90** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and cyclohexanecarboxylic acid (**72**) as the starting materials (88% yield). ^1H NMR (400 MHz, DMSO- d_6) δ 12.06 (s, 1H), 7.51 (dd, 1H, $J = 7.2, 2.8$ Hz), 7.39 (dd, 1H, $J = 6.6, 2.2$ Hz), 7.09 (m, 2H), 2.82 (tt, 1H, $J = 11.2, 3.8$ Hz), 2.03-1.99 (m, 2H), 1.82-1.77 (m, 2H), 1.72-1.67 (m, 1H), 1.65-1.55 (m, 2H), 1.44-1.34 (m, 2H), 1.31-1.23 (m, 1H).

2-Isobutyl-1H-benzo[d]imidazole (**91**)



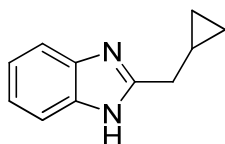
Compound **91** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and 3-methylbutanoic acid (**73**) as the starting materials (heated to 180°C) (74% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 12.14 (s, 1H), 7.45 (m, 2H), 7.10 (m, 2H), 2.66 (d, 2H, *J* = 7.6 Hz), 2.15 (m, 1H), 0.94 (s, 3H), 0.92 (s, 3H).

2-Isopentyl-1*H*-benzo[*d*]imidazole (**92**)



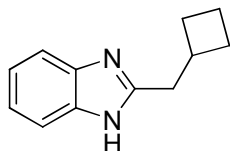
Compound **92** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and 4-methylpentanoic acid (**74**) as the starting materials (57% yield). ¹H NMR (400 MHz, DMSO-d₆) δ NH resonance not observed, 7.45 (m, 2H), 7.10 (m, 2H), 2.81 (t, 2H, *J* = 7.6 Hz), 1.66 (q, 2H, *J* = 7.4 Hz), 1.58 (m, 1H), 0.92 (s, 3H), 0.91 (s, 3H).

2-(Cyclopropylmethyl)-1*H*-benzo[*d*]imidazole (**93**)



Compound **93** was synthesized as described for compound **87** using benzene-1,2-diamine (**59**) and 2-cyclopropylacetic acid (**75**) as the starting materials (24% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 12.09 (s, 1H), 7.47 (m, 2H), 7.11 (m, 2H), 2.71 (d, 2H, *J* = 7.2 Hz), 1.15 (m, 1H), 0.50 (m, 2H), 0.28 (m, 2H).

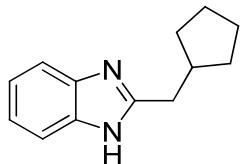
2-(Cyclobutylmethyl)-1*H*-benzo[*d*]imidazole (**94**)



Compound **94** was synthesized as described for compound **87** using benzene-1,2-diamine (**59**) and 2-cyclobutylacetic acid (**76**) as the starting materials (31% yield). ¹H NMR (400 MHz,

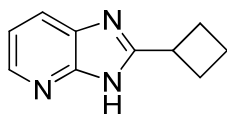
DMSO- d_6) δ 12.09 (s, 1H), 7.50 (d, 1H, $J = 7.2$ Hz), 7.38 (d, 1H, $J = 6.8$ Hz), 7.09 (m, 2H), 2.88 (d, 2H, $J = 7.6$ Hz), 2.77 (m, 1H), 2.08-2.01 (m, 2H), 1.87-1.73 (m, 4H).

2-(Cyclopentylmethyl)-1H-benzo[d]imidazole (95)



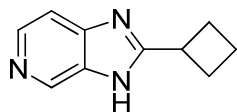
Compound **95** was synthesized as described for compound **78** using benzene-1,2-diamine (**59**) and 2-cyclopentylacetic acid (**77**) as the starting materials (31%). ^1H NMR (400 MHz, DMSO- d_6) δ NH resonance not observed, 7.62 (m, 2H), 7.30 (m, 2H), 2.94 (d, 2H, $J = 7.6$ Hz), 2.37 (qt, 1H, $J = 7.4$ Hz), 1.70 (m, 2H), 1.63 (m, 2H), 1.52 (m, 2H), 1.25 (m, 2H).

2-Cyclobutyl-3H-imidazo[4,5-b]pyridine (104)



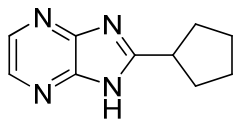
Compound **104** was synthesized as described for compound **78** using pyridine-2,3-diamine (**99**) and cyclobutanecarboxylic acid (**70**) as the starting materials (heated to 100°C) (77% yield). ^1H NMR (400 MHz, DMSO- d_6) δ 12.78 (bs, NH), 8.22 (bs, 1H), 7.83 (bs, 1H), 7.13 (dd, $J = 7.8, 5.0$ Hz, 1H), 3.70 (m, 1H), 2.46-1.84 (m, 6H). LRMS (ESI+) m/z : calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3$ 174.1, found 174.1 $[\text{M} + \text{H}]^+$.

2-Cyclobutyl-3H-imidazo[4,5-c]pyridine (105)



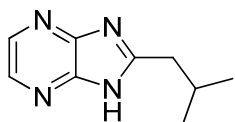
Compound **105** was synthesized as described for compound **78** using pyridine-3,4-diamine (**100**) and cyclobutanecarboxylic acid (**70**) as the starting materials (heated to 100°C) (25% yield). ^1H NMR (400 MHz, CDCl_3) δ NH resonance not observed, 8.95 (bs, 1H), 8.38 (d, 1H, $J = 13.0$ Hz), 7.50 (bs, 1H), 3.87 (m, 1H), 2.62-1.90 (m, 6H). LRMS (ESI+) m/z : calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3$ 174.1, found 174.4 $[\text{M} + \text{H}]^+$.

2-Cyclopentyl-1*H*-imidazo[4,5-*b*]pyrazine (107)



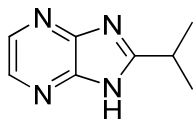
Compound **107** was synthesized as described for compound **78** using pyrazine-2,3-diamine (**101**) and cyclopentanecarboxylic acid (**71**) as the starting materials (heated to 120°C) (38% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.18 (s, 1H), 8.27 (s, 2H), 3.32 (m, 1H), 2.10-1.50 (m, 8H). LRMS (ESI+) *m/z*: calcd for C₁₀H₁₂N₄ 189.1, found 189.1 [M + H]⁺.

2-Isobutyl-1*H*-imidazo[4,5-*b*]pyrazine (108)



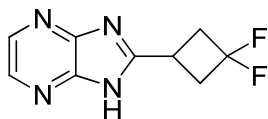
Compound **108** was synthesized as described for compound **78** using pyrazine-2,3-diamine (**101**) and 3-methylbutanoic acid (**73**) as the starting materials (heated to 120°C) (71% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.22 (s, 1H), 8.27 (s, 2H), 2.74 (d, 2H, *J* = 7.4 Hz), 2.20 (m, 1H), 0.93 (d, 6H, *J* = 6.4 Hz). LRMS (ESI+) *m/z*: calcd for C₉H₁₂N₄ 177.1, found 177.2 [M + H]⁺.

2-Isopropyl-1*H*-imidazo[4,5-*b*]pyrazine (109)



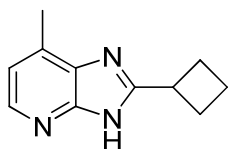
Compound **109** was synthesized as described for compound **78** using pyrazine-2,3-diamine (**101**) and isobutyric acid (**102**) as the starting materials (heated to 120°C) (40% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.20 (bs, 1H), 8.29 (bs, 2H), 3.19 (m, 1H), 1.35 (d, *J* = 6.4 Hz, 6H). LRMS (ESI+) *m/z*: calcd for C₈H₁₀N₄ 163.1, found 163.0 [M + H]⁺.

2-(3,3-Difluorocyclobutyl)-1*H*-imidazo[4,5-*b*]pyrazine (110)



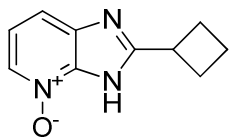
To a solution of carbonyldiimidazole (8.5 g, 52.5 mmol) in ACN (25 mL) was added 3,3-difluorocyclobutanecarboxylic acid (**103**, 7.5g, 55 mmol,; A Practical Synthesis of 3,3-Difluorocyclobutane Carboxylic Acid: Elend, D.; Fengas, D.; Fray, M. J. Synthetic Communication, 2005, 35, 657-662) in portions. After warming the reaction to 50°C for 15 min, pyrazine-2,3-diamine (**101**, 5.5 g, 50 mmol) was added. The mixture was then heated at 90°C for 6 h. After cooling to 25°C, the precipitate was isolated by filtration and washed with ACN (30 mL) to give 7.5 g (72%) of 2-(3,3-difluorocyclobutyl)-1*H*-imidazo[4,5-*b*]pyrazine (**110**) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.41 (s, 1H), 8.33 (s, 2H), 3.67 (m, 1H), 3.20-3.05 (m, 4H). LRMS (ESI+) *m/z*: calcd for C₉H₁₂N₄ 177.1, found 177.2 [M + H]⁺.

2-Cyclobutyl-7-methyl-3*H*-imidazo[4,5-*b*]pyridine (**113**)



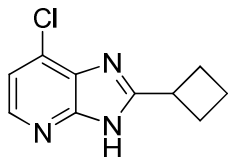
Compound **113** was synthesized as described for compound **78** using 4-methylpyridine-2,3-diamine (**112**) and cyclobutanecarboxylic acid (**70**) as the starting materials (heated to 100°C) (53% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.67 (bs, 1H), 8.03 (d, 1H, *J* = 4.4 Hz), 6.94 (d, 1H, *J* = 4.8 Hz), 3.67 (m, 1H), 2.50 (s, 3H), 2.55-1.72 (m, 6H). LRMS (ESI+) *m/z*: calcd for C₁₁H₁₃N₃ 188.1, found 188.4 [M + H]⁺.

2-Cyclobutyl-3*H*-imidazo[4,5-*b*]pyridine 4-oxide (**114**)



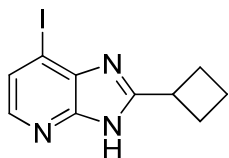
meta-Chloroperbenzoic acid (15 g, 62 mmol) was added to a solution of 2-cyclobutyl-3*H*-imidazo[4,5-*b*]pyridine (**104**, 9.5 g, 55 mmol) in Acetone (300 mL) and the reaction mixture was stirred at 25°C for 16 h. The slurry was filtered and the filtered solid was washed with acetone (50 mL) and dried under reduced pressure to give 8.8 g (84%) of 2-cyclobutyl-3*H*-imidazo[4,5-*b*]pyridine 4-oxide. ¹H NMR (400 MHz, D₂O) δ 7.98 (m, 1H), 7.51 (m, 1H), 7.06 (m, 1H), 3.64 (m, 1H), 2.3-1.7 (m, 6H). LRMS (ESI+) *m/z*: calcd for C₁₀H₁₁N₃O 190.1, found 190.0 [M + H]⁺.

7-Chloro-2-cyclobutyl-3H-imidazo[4,5-*b*]pyridine (**115**)



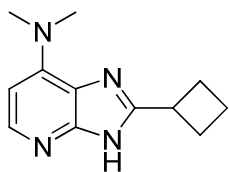
POCl₃ (50 mL, 330 mmol) was added to 2-cyclobutyl-3H-imidazo[4,5-*b*]pyridine 4-oxide (**114**, 8.5 g, 45 mmol) and the reaction mixture was refluxed for 2 h. The solution was cooled to 40°C and concentrated under reduced pressure. The residue was taken up in DCM (300 mL) and pH 9 phosphate aqueous buffer (400 mL, 1N K₂HPO₄). The organic layer was isolated, dried (MgSO₄), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (50% to 75% EtOAc/Hexanes) afforded 7 g (75%) of 7-chloro-2-cyclobutyl-3H-imidazo[4,5-*b*]pyridine (**116**). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.14 (s, 1H), 8.15 (d, 1H), 7.28 (d, 1H), 3.72 (m, 1H), 2.5-1.8 (m, 6H). LRMS (ESI+) *m/z*: calcd for C₁₀H₁₀ClN₃ 208.1, found 208.2 [M + H]⁺.

2-Cyclobutyl-7-iodo-3H-imidazo[4,5-*b*]pyridine (**116**)



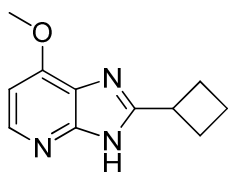
A mixture of 7-chloro-2-cyclobutyl-3H-imidazo[4,5-*b*]pyridine (**115**, 5.2 g, 25 mmol), NaI (11.2 g, 75 mmol), and TMS-Cl (8.1 g, 75 mmol) in ACN (200 mL) was refluxed for 18 h. The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (250 mL) and washed with aqueous NaOH (2M, 150 mL). The aqueous layer was back extracted with EtOAc (200 mL). The organics were combined, dried, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50:1 DCM/MeOH) to afford 5.1 g (67%) of 2-cyclobutyl-7-iodo-3H-imidazo[4,5-*b*]pyridine (**116**) as a white solid. LRMS (ESI+) *m/z*: calcd for C₁₀H₁₀IN₃ 300.0, found 300.0 [M + H]⁺.

2-Cyclobutyl-*N,N*-dimethyl-3H-imidazo[4,5-*b*]pyridin-7-amine (**117**)



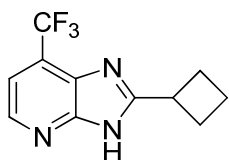
Dimethylamine (2 mL, 2M in THF) was added to 7-chloro-2-cyclobutyl-3*H*-imidazo[4,5-*b*]pyridine (**115**, 0.21 g, 1 mmol) in a 4 mL vial. The vial was sealed and the reaction mixture was heated to 110°C for 18 h. The reaction mixture was cooled and a white solid precipitated. The slurry was diluted with Et₂O (10 mL) and filtered. The solid was triturated with H₂O (5 mL), filtered, and dried under reduced pressure to give 110 mg (51%) of 2-cyclobutyl-*N,N*-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-7-amine (**117**). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.38 (s, 1H), 7.79 (d, 1H, *J* = 5.6 Hz), 6.20 (d, 1H, *J* = 5.6 Hz), 3.60 (m, 1H), 3.30 (s, 6H), 2.42-1.80 (m, 6H). LRMS (ESI+) *m/z*: calcd for C₁₂H₁₆N₄ 217.1, found 217.0 [M + H]⁺.

2-Cyclobutyl-7-methoxy-3*H*-imidazo[4,5-*b*]pyridine (**118**)



Sodium methoxide (3 mL, 35 wt%, in MeOH) was added to 7-chloro-2-cyclobutyl-3*H*-imidazo[4,5-*b*]pyridine (207 mg, 1 mmol) and the resulting mixture was heated to 150°C for 3 h. The reaction was then quenched with phosphate buffer (1M, pH 7, 50 mL) and extracted with DCM (4 x 25 mL). Purification by silica gel chromatography (0% to 20% MeOH/EtOAc) gave 106 mg (52%) of 2-cyclobutyl-7-methoxy-3*H*-imidazo[4,5-*b*]pyridine as a white solid. LRMS (ESI+) *m/z*: calcd for C₁₁H₁₃N₃O 204.1, found 204.1 [M + H]⁺.

2-Cyclobutyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (**119**)



KF (170 mg, 2.93 mmol) and CuI (570 mg, 3.00 mmol) were combined into a sealed tube and heated under reduced pressure while being gently shaken until a homogeneously greenish

powder was obtained. After the addition of 2-cyclobutyl-7-iodo-3*H*-imidazo[4,5-*b*]pyridine (**116**, 580 mg, 1.94 mmol), TMSi-CF₃ (710 mg, 5.00 mmol), and DMF (10 mL) the suspension was heated to 55°C for 18 h with vigorous stirring. The reaction mixture was poured into aqueous ammonia (12%, 50 mL) and extracted with EtOAc (2 x 80 mL). The organics were combined, washed with brine (2 x 50 mL), dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (50:1 DCM/MeOH) to afford 170 mg (36%) of 2-cyclobutyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (**119**) as a white solid. LRMS (ESI+) *m/z*: calcd for C₁₁H₁₀F₃N₃ 242.1, found 242.0 [M + H]⁺.

Biological Methods

Low Temperature SDS-PAGE: RAW 264.7 cells were seeded into 6-well dishes at a density of 1.5×10^6 cells/well in 2 mL of growth media. Cells were incubated for 2-3 h at 37°C and 10% CO₂. Next, 1 mL of media was removed from each well and replaced with 1 mL of a 2X cocktail containing IFN γ (100 U/mL final), LPS (2 μ g/mL final) and compound or vehicle (0.1% DMSO final) diluted in DMEM without serum. Cells were incubated overnight (~15 hr) at 37°C and 10% CO₂. Cells were washed once with ice cold PBS and then 200 μ L of ice-cold lysis buffer containing protease inhibitors was added to each well. Cells were scraped from the dish and transferred to micro-centrifuge tubes on ice. Samples were sonicated for 5 seconds at setting 4 and centrifuged for 10 minutes at 4°C. Supernatants were transferred to clean tubes and stored on ice. The concentration of protein in the cell extracts was determined using a Bradford assay with a BSA standard curve as described by the manufacturer (Advanced). Equivalent amounts of protein extracts were added to micro-centrifuge tubes and the volume was adjusted to 10 μ L with lysis buffer. An equal volume of ice-cold 2X loading buffer was added to each sample and gently pipetted to mix. Samples were stored on ice until ready to load. Twenty microliters of each sample was loaded onto a 15-well 4-20% Tris-glycine polyacrylamide gel. The gel was run in pre-chilled 1X SDS running buffer in a cold room for 2.5 h at 125 V. Proteins were transferred to nitrocellulose for 2.5 h at 70 V in 1X transfer buffer. The membrane was blocked overnight in Blotto diluted in western wash buffer at 4°C. The membrane was incubated in a 1:2500 dilution of mouse anti-iNOS antibody (BD Biosciences) in Blotto for 1 h at room temperature followed by 3 x 5 min washes in western wash buffer. The blot was then incubated in a 1:2000 dilution of goat anti-mouse HRP-conjugated secondary antibody (Santa Cruz

Biotech) in Blotto for 1 hour at room temperature. Following 4 x 5 min washes, the proteins were visualized by chemiluminescence using West Dura detection reagent as described by the manufacturer (Pierce). The data were captured on a CCD-based imaging device (Alpha Inotech).

Mouse Pharmacokinetics: Male (Balb/c) mice (6 to 8 weeks of age) were obtained from Charles-River Laboratories (Hollister, CA). Animals were acclimated for a minimum of 3 days prior to performing any experimental procedures. A 12-hr light: 12-hr dark cycle was maintained throughout the course of all experiments in a temperature and humidity controlled vivarium facility. Animals were fed standard laboratory rodent chow, and water *ad libitum*. For intravenous (IV) administration, 12 overnight fasted animals received a single dose of 3 or 1 mg/kg body weight (3 or 1 mL/kg) via penile vein injection under light isoflurane anesthesia in 10% DMSO; 30% PEG-400 and 60% HP β CD (30% w/v in water). For oral (PO) administration, 9 overnight fasted animals received a single dose of 10 mg/kg body weight (10 mL/kg) via oral gavage in a suspension of 0.5% Tween-80, 0.5% PVP-K30, 9% PEG-400 and 90% CMC in water (0.5% w/v). PO dose suspensions were dispersed with an electric homogenizer, followed by treatment with a sonicator probe on wet ice. Blood samples (~ 125 μ L) were collected by puncture of the submandibular vein (i.e. the cheek pouch method) into lithium heparin pre-treated tubes at 0 (pre-dose), 5, 10, 20 and 40 minutes, 1, 2, 4, 8, 12 and 24 hours following IV administration and at 0 (pre-dose), 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hours post-dose following PO administration, such that no animal was sampled more than 3 times. Plasma was isolated by centrifugation and stored at -80°C until analysis by LC-MS/MS.

Sample analyses were performed by LC-MS using a PE Sciex API 4000 Q-Trap mass spectrometer tandem with Agilent 1100 chromatography system. Polar-RP Synergi column from

Phenomenex (2.0 x 3.0 mm, 4.0 micron). Chromatography was performed using a gradient system using two mobile phases A and B. The mobile phase A consisted of 0.1% formic acid in water and mobile phase B of 0.1% formic acid in acetonitrile. Mobile phase B was ramped from 0% to 100% from 0.0 to 1.0 min and was held at 100% B from 1.0 to 1.9 min. From 2.0 to 2.7 min, column was equilibrated to the initial condition at 100% A. Flow rate for the gradient was set at 1.0 mL/min. Mass spectrometry detection was carried out on a PE Sciex API4000 Q-Trap equipped with a Turbo IonSpray source. ESI+ mass spectra were acquired with multiple reaction monitoring (MRM). The plasma samples were prepared by protein precipitation monitored with an internal standard. Standard curve was prepared by spiking control plasma with the compound and serial dilutions from this spiked solution generated different levels of the standard curve. A weighted linear least squares regression was then performed to generate a correlation between concentration and the relative amounts of analyte and internal standard for compound. Twelve standard curve were used, highest level at 10,000 ng/mL. Lowest level of detection was at 4.0 ng/mL.

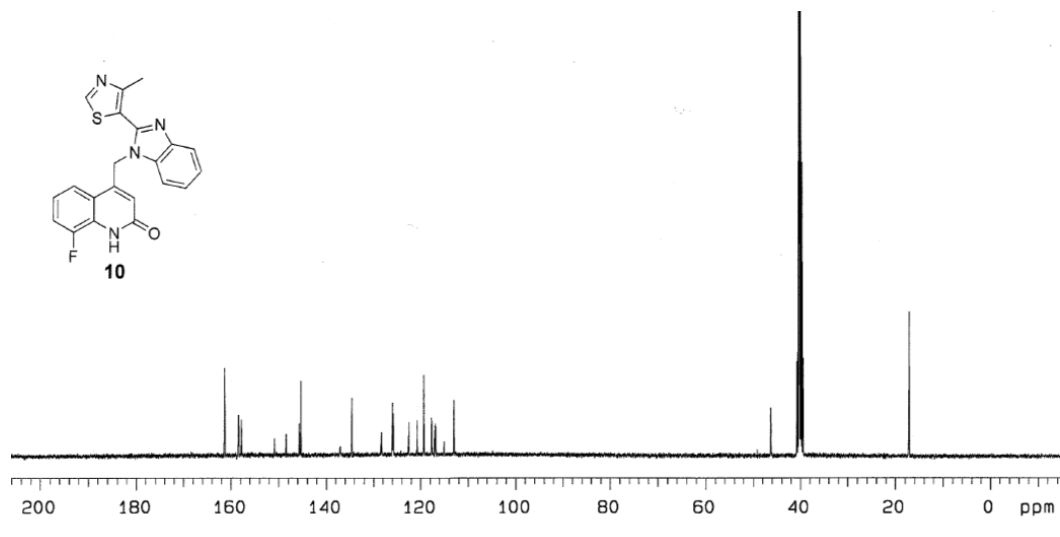
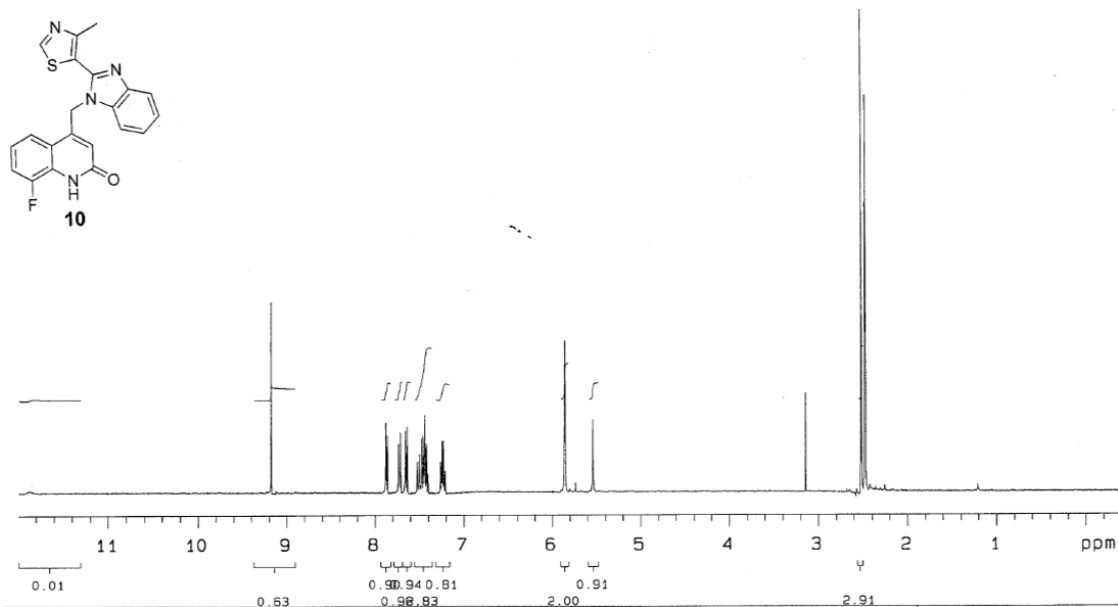
Mouse Liver Microsome Assay: Test article in DMSO was added to incubation buffer such that the final DMSO concentration was 0.4% (v/v). Microsomes were stored at -70°C until use, thawed on ice and then diluted to 5 mg/mL in Phosphate buffer immediately before use. Microsome incubations were performed in 100 mM Phosphate buffer (pH 7.4), containing 0.1% BSA (fatty acid free), 1 mM EDTA, 3 mM MgCl₂, alamethicin (50 µg/mg microsomal protein) and 1.25 mM D-Saccharic acid 1,4-lactone. D-saccharic acid 1,4-lactone is an inhibitor of β-glucuronidase, an enzyme which can rapidly hydrolyze glucuronide conjugates. Microsomes and test article in incubation buffer were pre-warmed in triplicate at 37°C for 5 minutes.

Reactions were initiated by addition of 25 μ L of NADPH-regenerating system (consisting of 20 mM NADP, 100 mM glucose-6-phosphate, 20 U/mL glucose-6-phosphate dehydrogenase and 100 mM UDPGA). Final incubation volume was 0.5 mL with a test article concentration of 5 μ M. At specified time points, 100 μ L aliquots were removed and combined with 300 μ L of chilled quenching reagent (1:2 water: acetonitrile) containing internal standard (IS). Sample plates were then centrifuged at 1,500 g for 15 minutes and supernatants submitted for LC-MS/MS analysis. Relative test article concentrations were defined by the analyte/IS peak ratios in each sample.

Cytochrome P450 Inhibition Assay: Compounds were evaluated for biochemical inhibition of cytochrome P450 using the Vivid CYP450 Blue assay (Invitrogen) adapted to 1536-well plate format. Briefly, individual isozymes and their blue substrates were diluted to a 2X working concentration in 1X assay buffer. Isozyme concentrations were: 3A4, 10 nM; 2D6, 40 nM; 1A2, 12 nM; 2C9, 20 nM; and 2C19, 10 nM. 2X Regeneration System was included in the isozyme mix. Substrate concentrations were: 40 nM for 3A4 and 2D6; 20 μ M for 1A2, 2C9, and 2C19. NADP⁺ was added to the substrate mix at a concentration of 400 μ M for the assays. A volume of 2.5 μ L of the isozyme mix was dispensed into black Greiner 1536-well plates. Then, 30 nL of compound was added to the wells. Subsequently, 2.5 μ L of the blue substrate was added and plates were incubated for 1 hour at room temperature. Four replicate data points are obtained per compound at each concentration. Inhibition of substrate turnover was measured using a fluorescent plate reader with excitation at 405 nm and emission at 450 nm (Molecular Devices).

^1H NMR, ^{13}C NMR (when available), and LC trace (for purity).

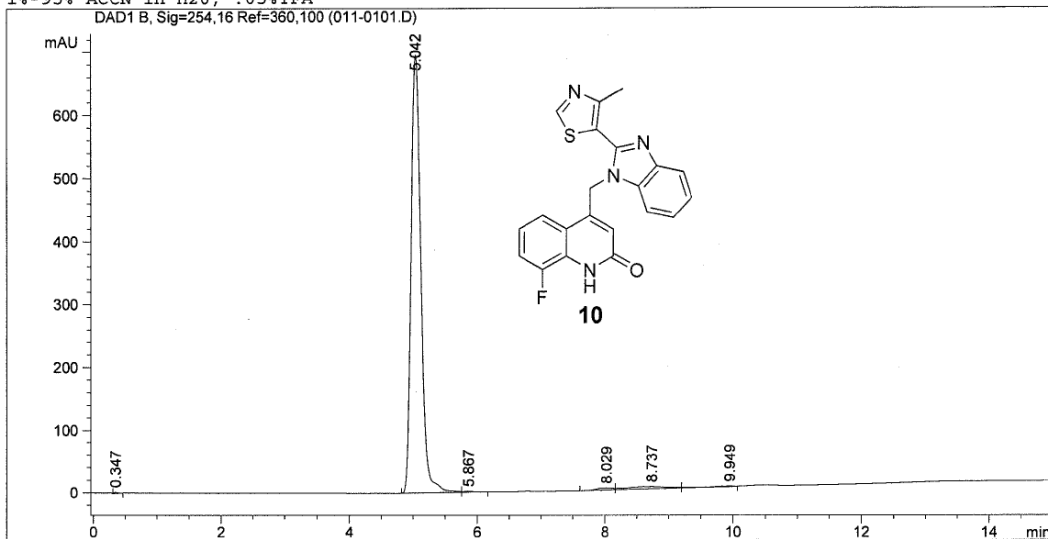
Compound 10: 8-Fluoro-4-((2-(4-methylthiazol-5-yl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)quinolin-2(1*H*)-one



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Acq. Instrument : Kalypsys                   Inj Volume: 5 µl
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Use Multiplier & Dilution Factor with ISTDs

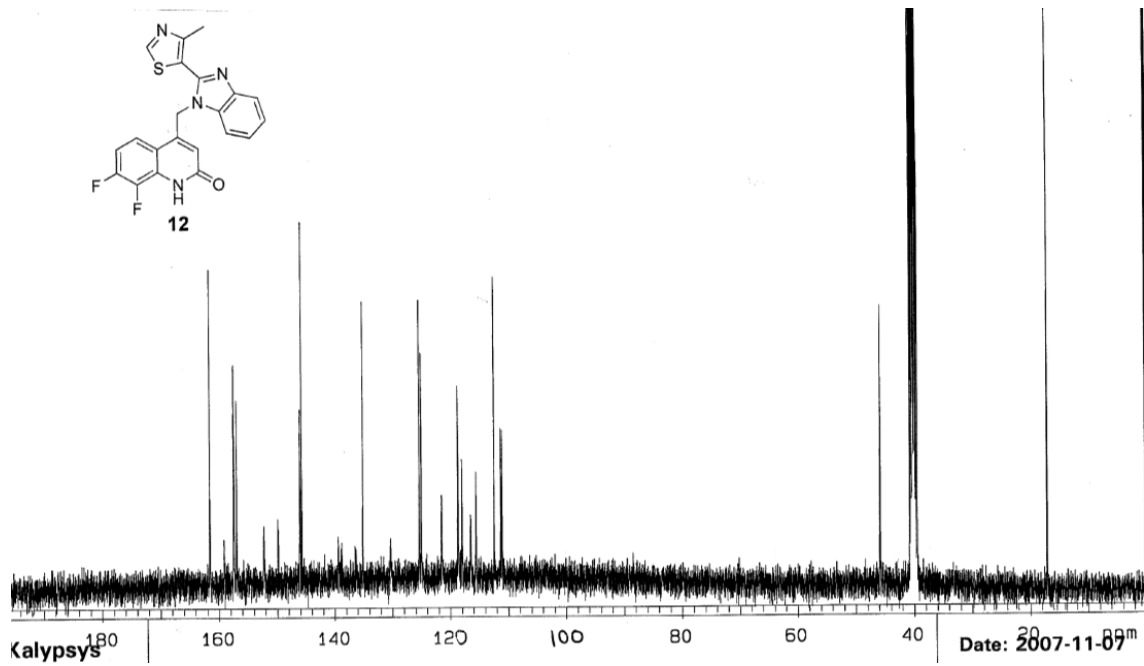
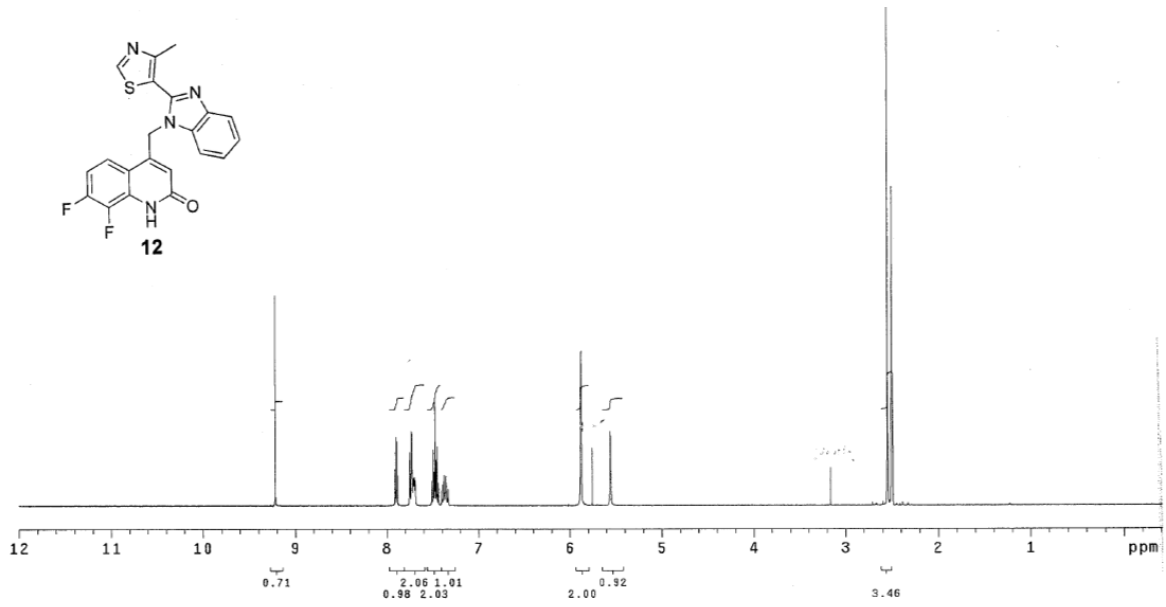
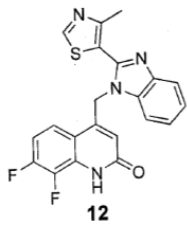
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Signal 1: DAD1 B, Sig=254,16 Ref=360,100

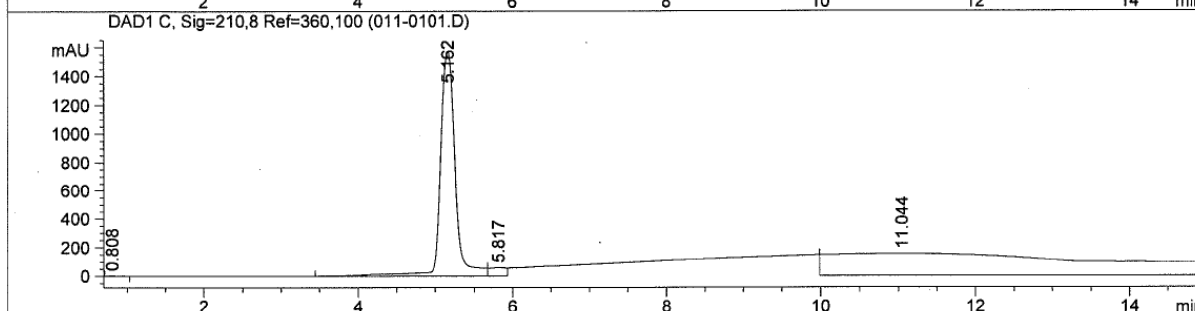
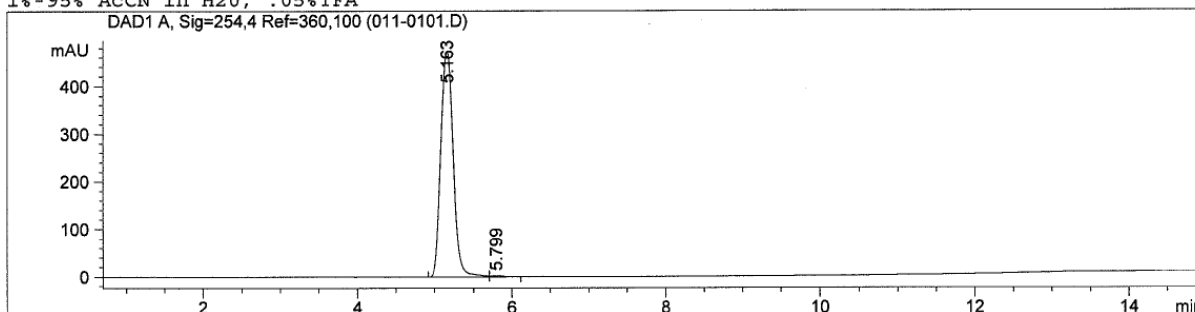
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2	5.042	BB	0.1650	7331.71484	695.63721	96.1924
3	5.867	BB	0.1783	21.39340	1.66104	0.2807
4	8.029	BV	0.2664	55.19286	3.11976	0.7241
5	8.737	VV	0.5214	153.50287	3.58595	2.0140
6	9.949	VV	0.4583	52.77196	1.41759	0.6924

Totals : 7621.92926 707.41003

Compound 12: 7,8-Difluoro-4-((2-(4-methylthiazol-5-yl)-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one



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Acq. Instrument : Kalypsys Inj Volume : 5 µl
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1%-95% AcCN in H2O, .05%TFA



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Area Percent Report
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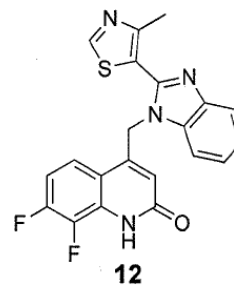
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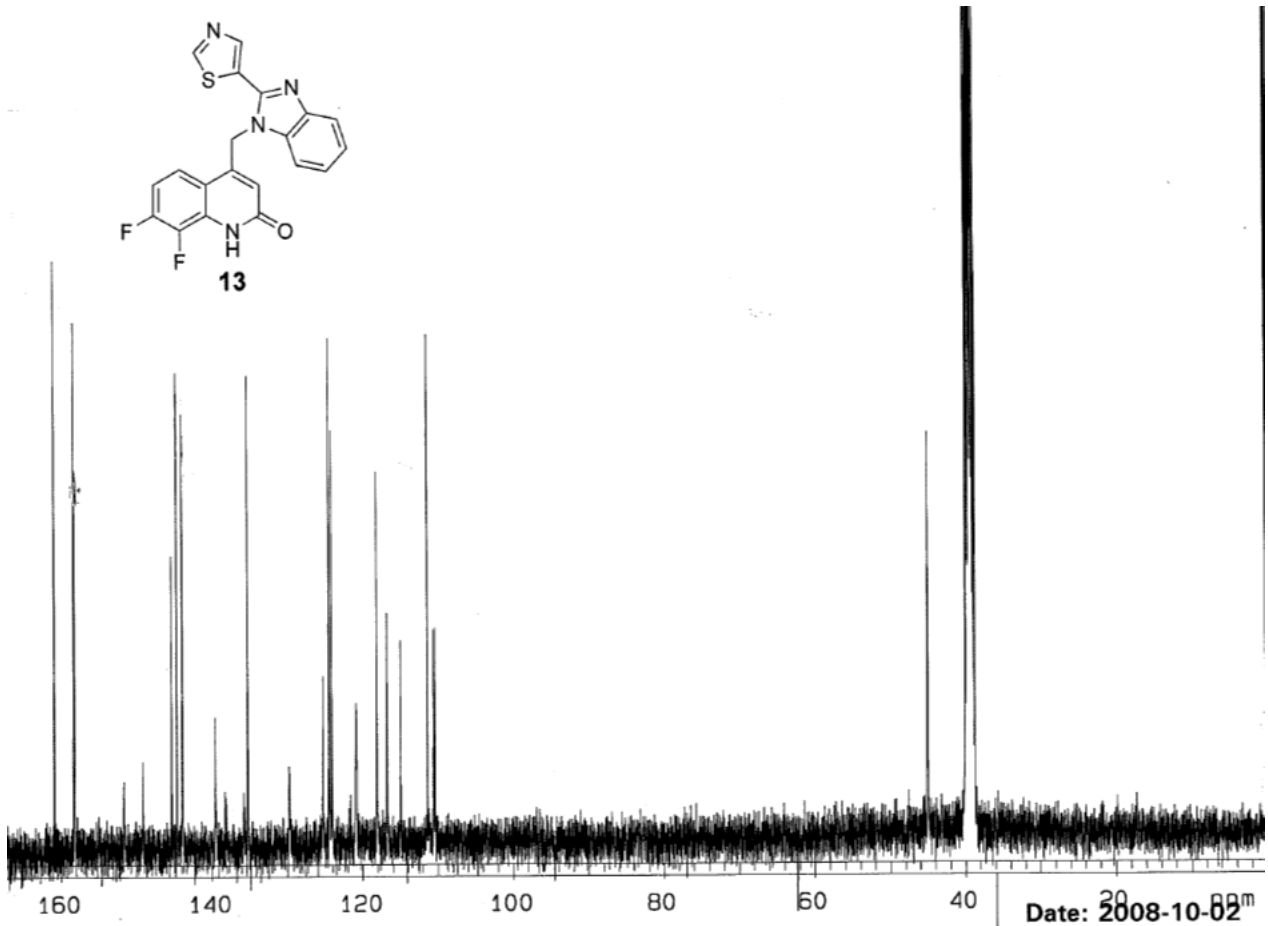
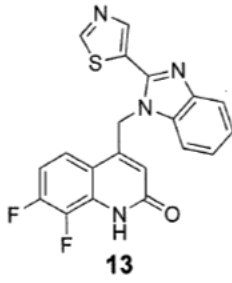
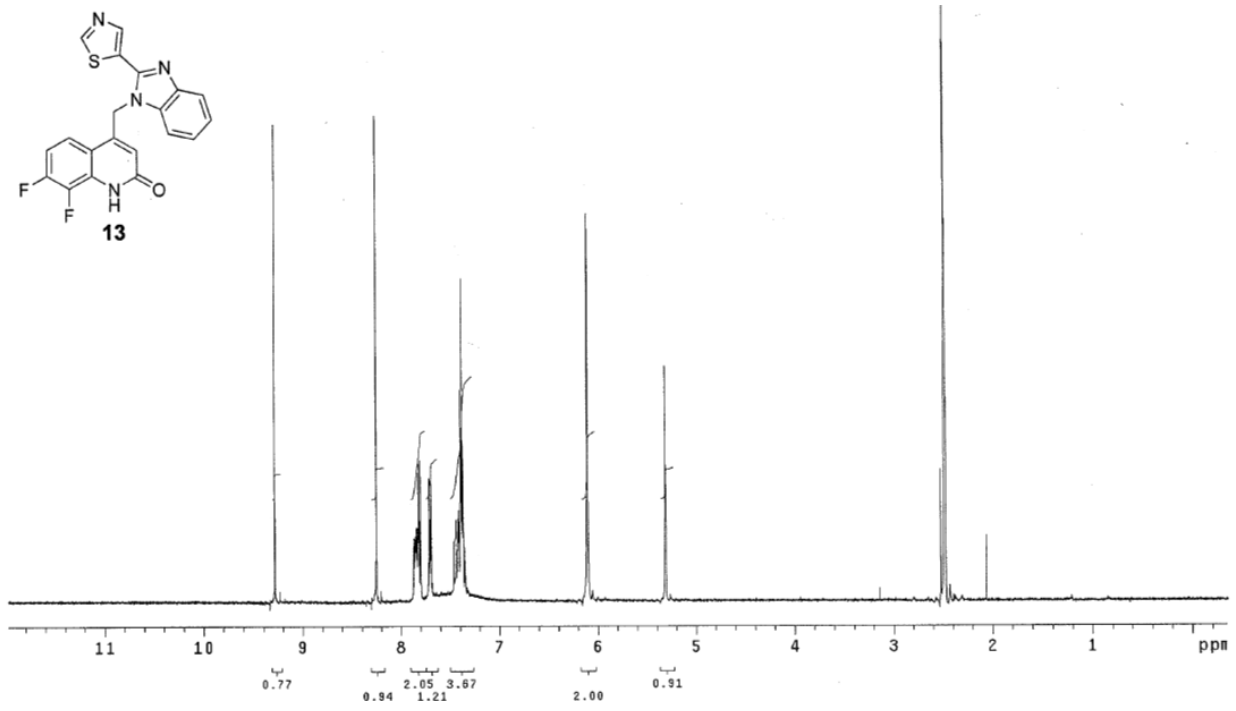
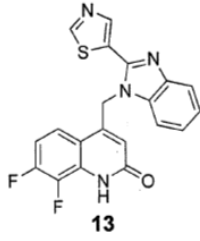
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Totals : 5284.20066 476.55516

Signal 2: DAD1 C, Sig=210,8 Ref=360,100



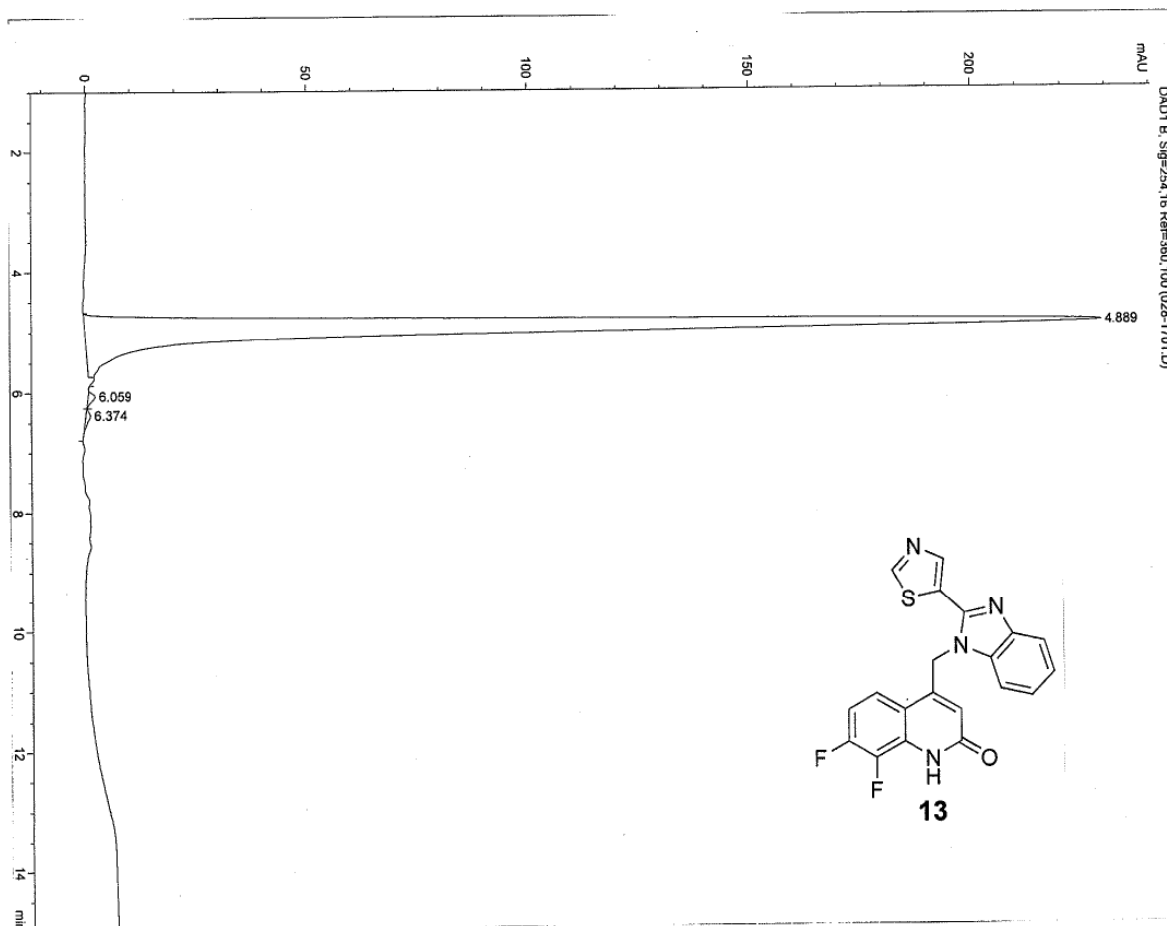
Compound 13: 7,8-Difluoro-4-((2-(thiazol-5-yl)-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one



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Acq. Instrument : Kalypsys                      Inj Volume: 5 µl
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1%-95% AccN in H2O, .05%TFA
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Area Percent Report

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Use Multiplier & Dilution Factor with ISTDs

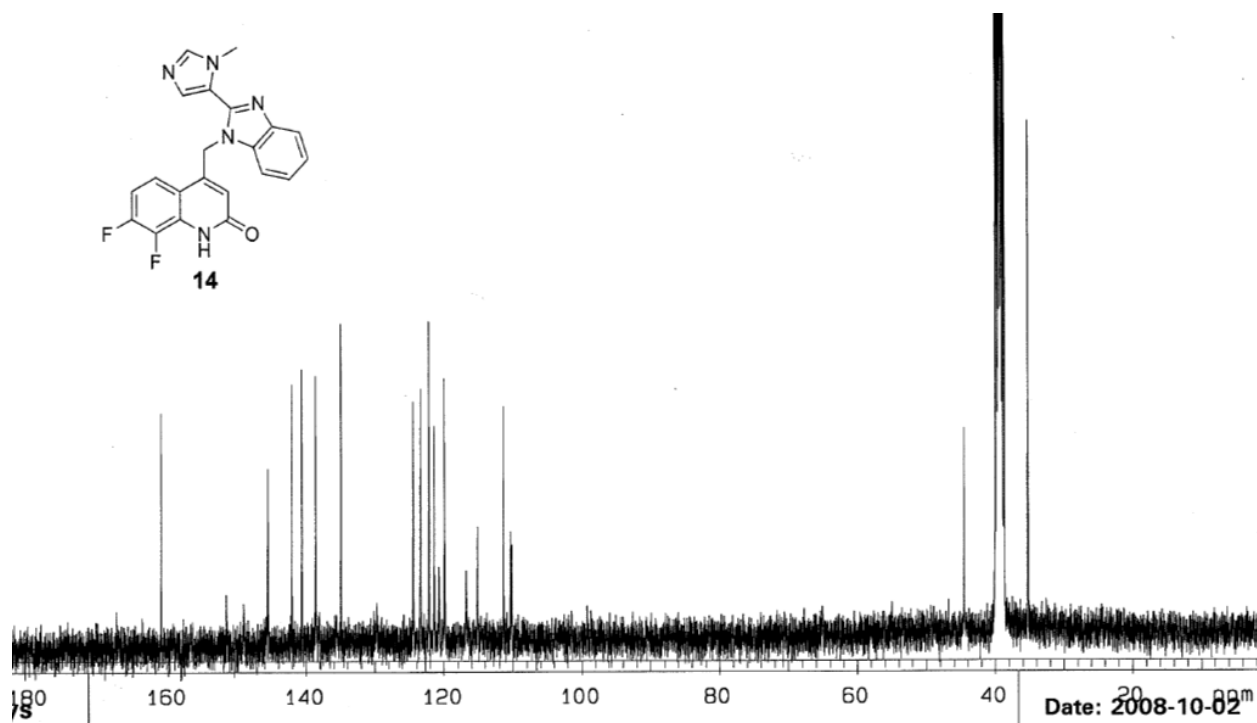
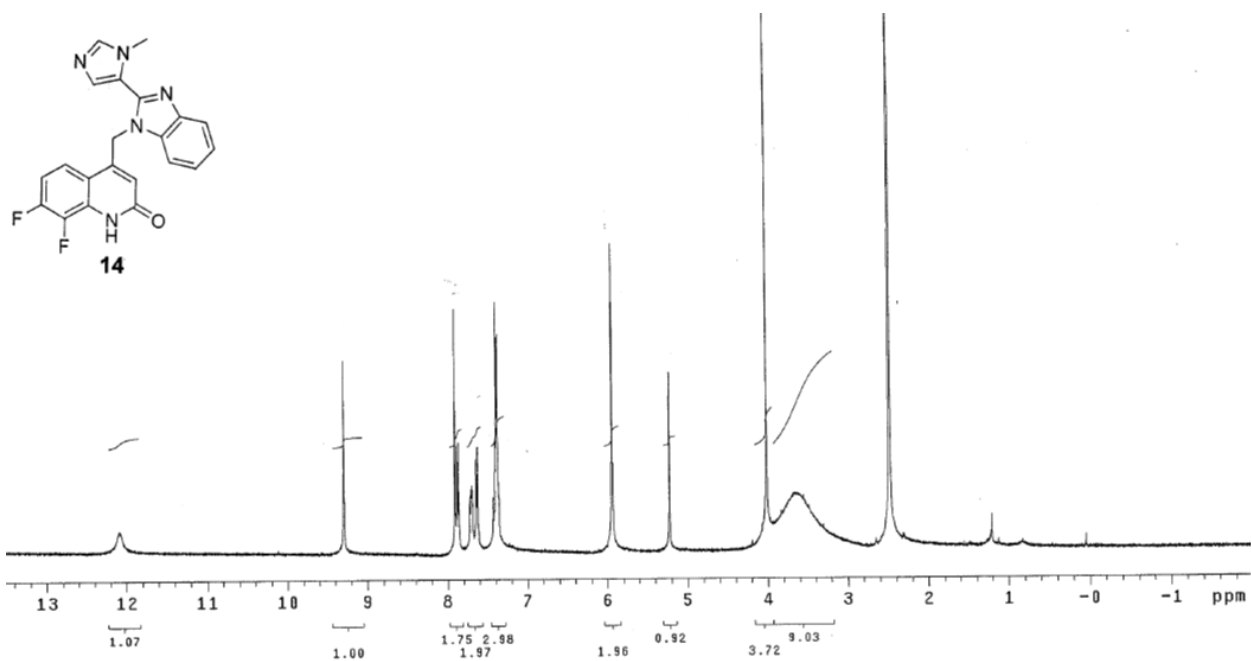
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Signal 1: DAD1 B, Sig=254,16 Ref=360,100

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1	4.889	BB	0.2277	3415.59131	229.39148	99.2171
2	6.059	BV	0.1406	13.73321	1.56095	0.3989
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Totals : 3442.54383 232.04919

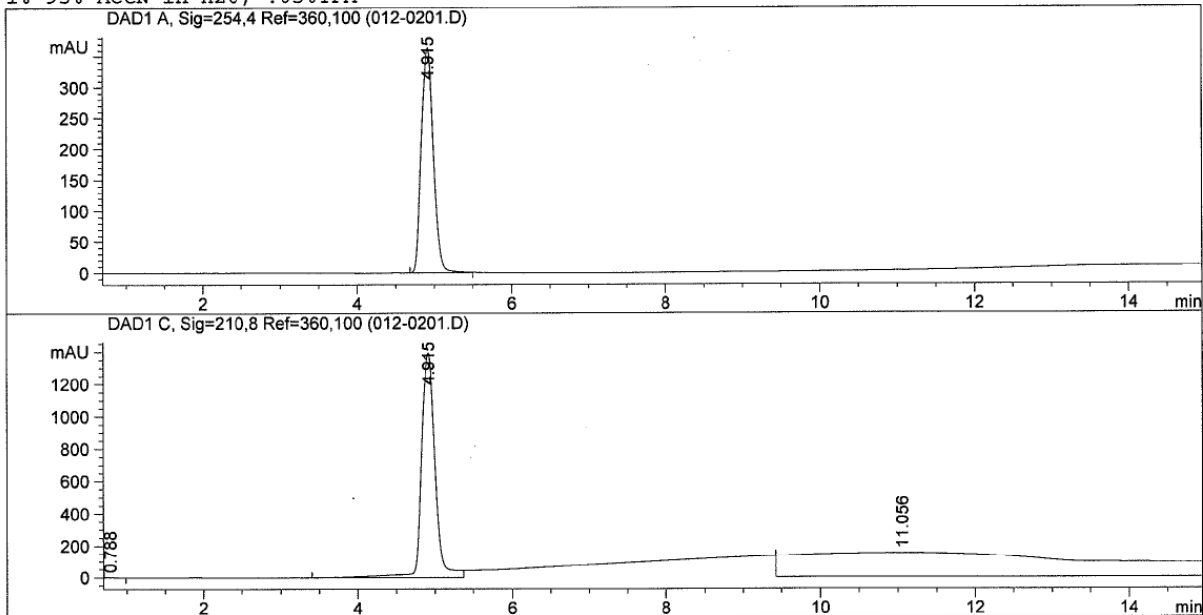
Compound 14: 7,8-Difluoro-4-((2-(1-methyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one



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Acq. Instrument : Kalypsys                  Inj Volume : 5 µl
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Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/5/2007 1:18:30 PM by 14
1%-95% AccN in H2O, .05%TFA

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Area Percent Report
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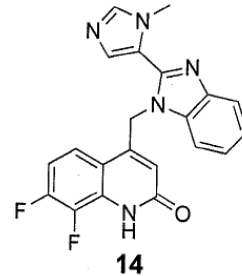
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Use Multiplier & Dilution Factor with ISTDs

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Signal 1: DAD1 A, Sig=254,4 Ref=360,100

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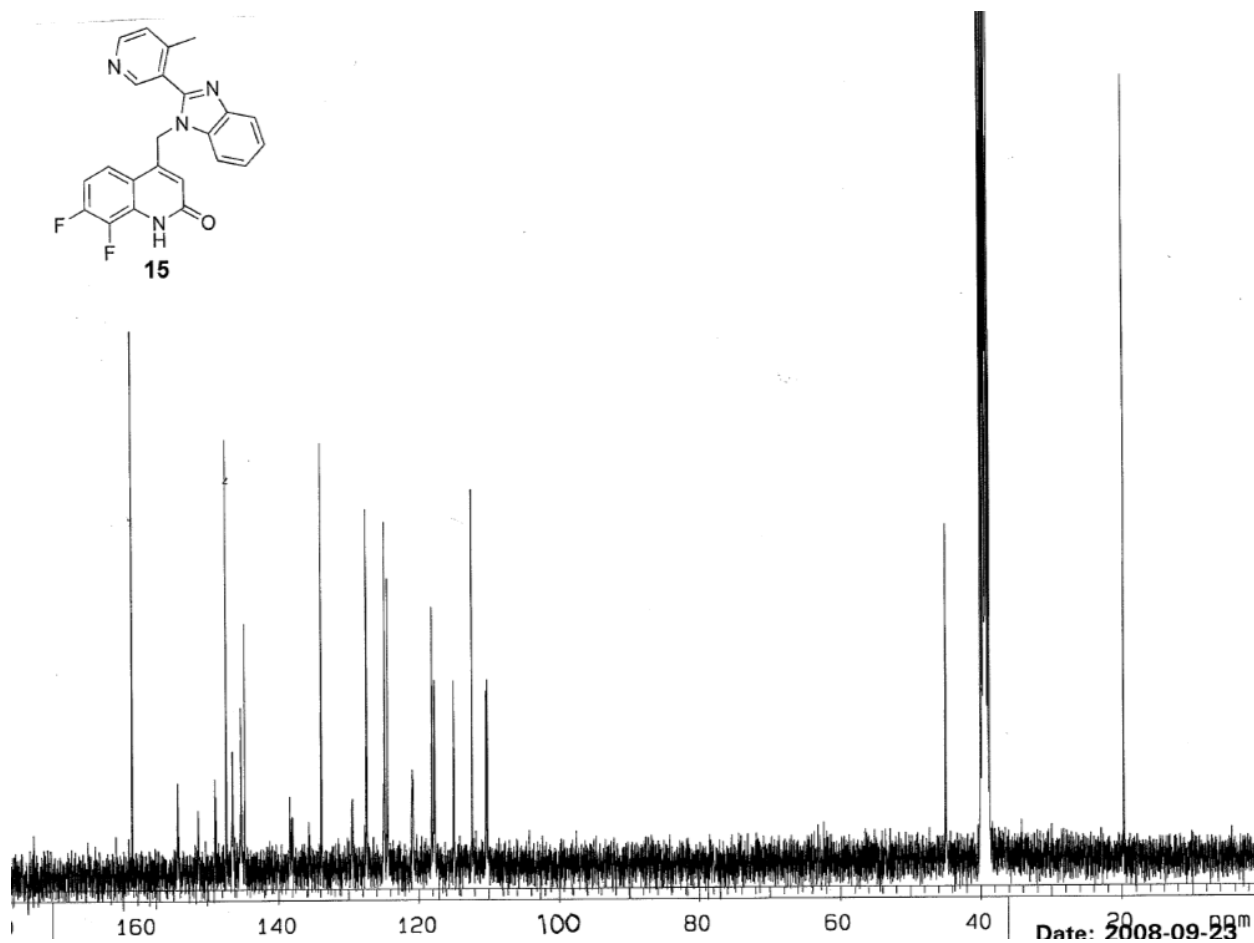
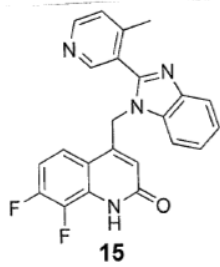
Totals : 4066.20752 364.46320



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

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1	0.788	BB	0.0971	10.28843	1.59770	0.0174
2	4.915	BV	0.2013	1.75989e4	1394.12976	29.6990
3	11.056	BBA	3.2062	4.16484e4	152.21223	70.2837

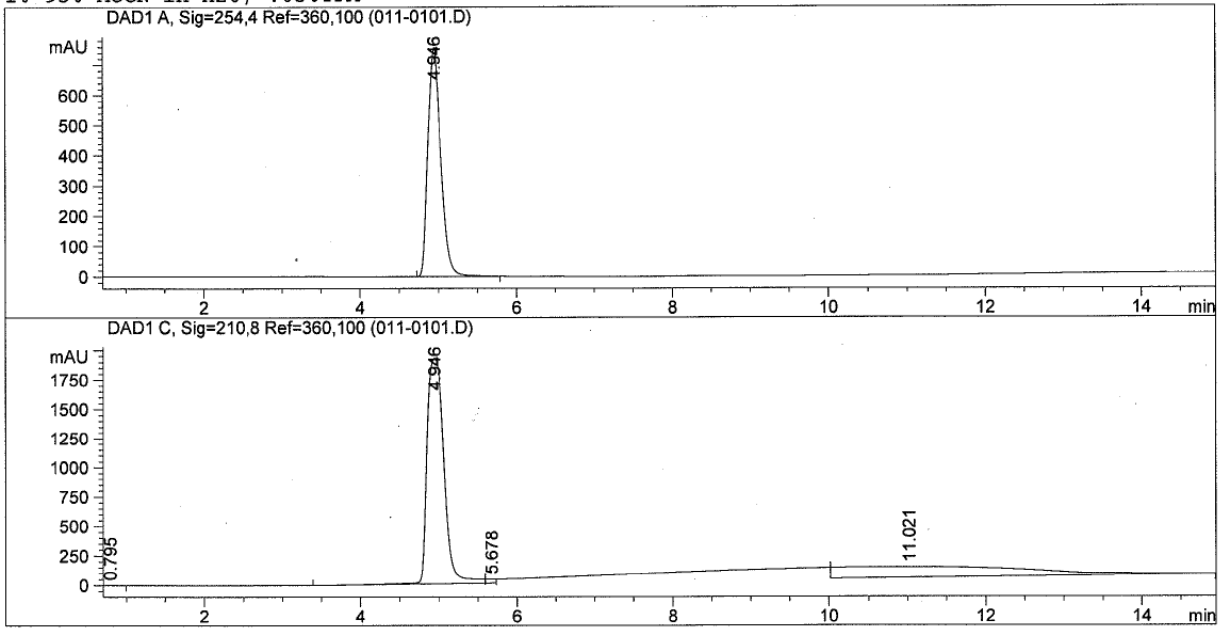
Compound 15: 7,8-Difluoro-4-((2-(4-methylpyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one



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Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/5/2007 1:18:30 PM by 14
1%-95% AcCN in H2O, .05%TFA

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Area Percent Report
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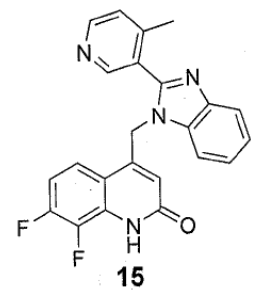
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Use Multiplier & Dilution Factor with ISTDs

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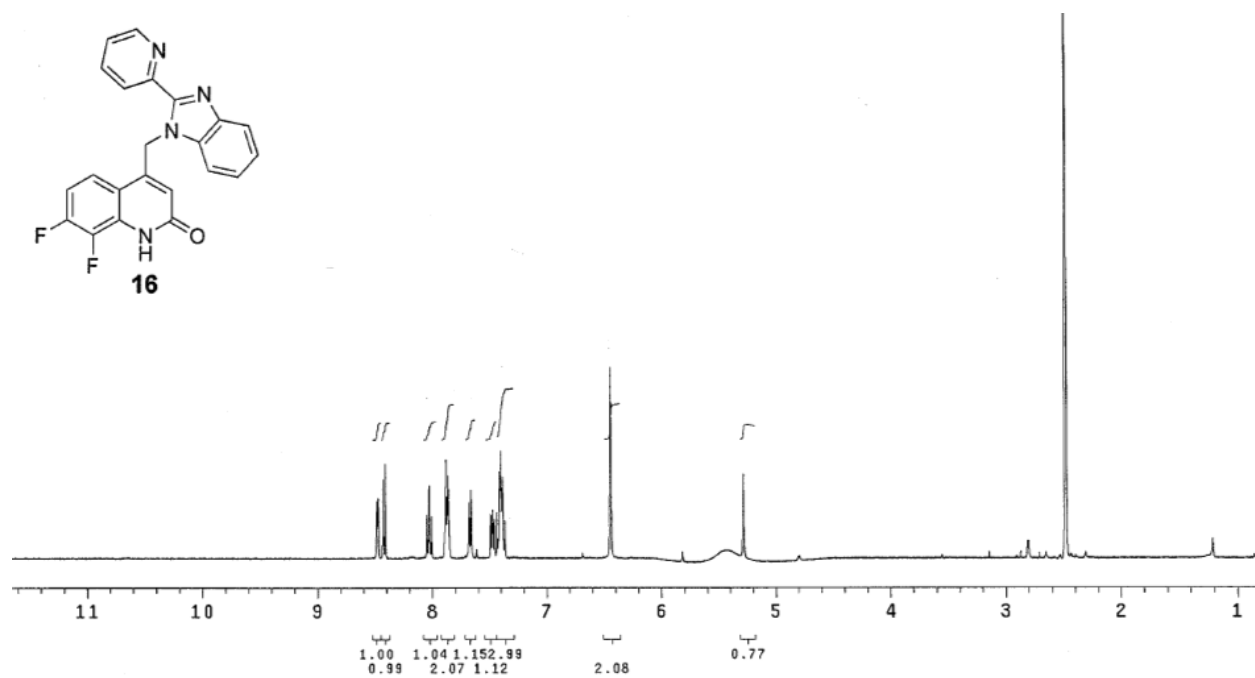
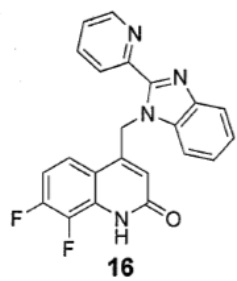
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.946	BB	0.1837	8810.47363	757.45343	100.0000

Totals : 8810.47363 757.45343



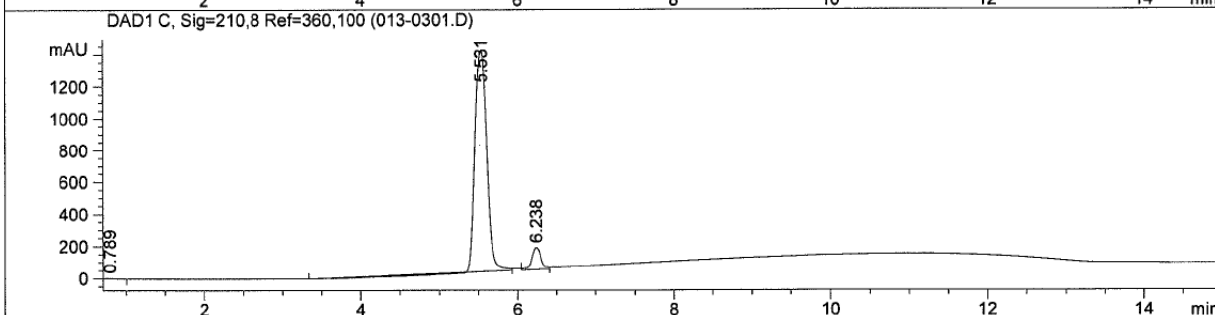
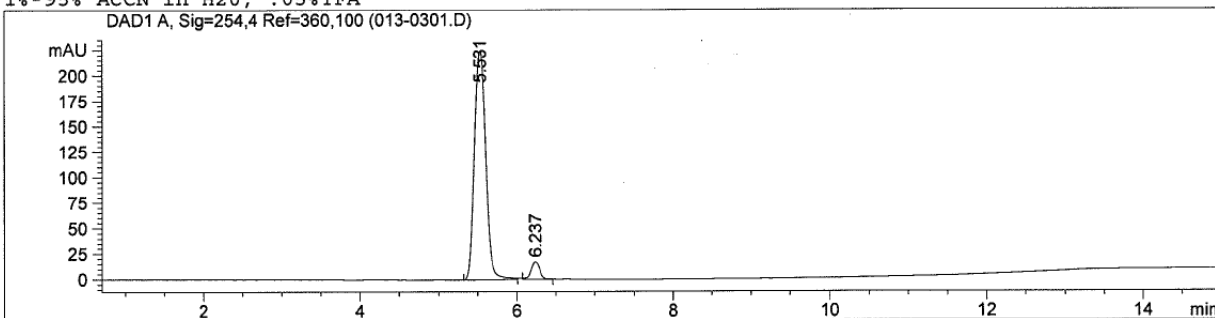
Compound 16: 7,8-Difluoro-4-((2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one



```

=====
Injection Date   : 11/5/2007 2:14:21 PM           Seq. Line :    3
Sample Name     :                               Location  : Vial 13
Acq. Operator   : 14                             Inj       :    1
Acq. Instrument : Kalypsys                        Inj Volume: 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 11/5/2007 1:18:30 PM by 14
1%-95% AcCN in H2O, .05%TFA

```



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Area Percent Report
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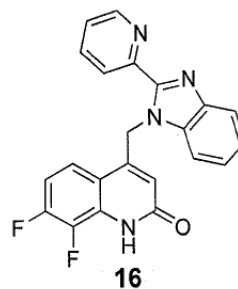
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

```

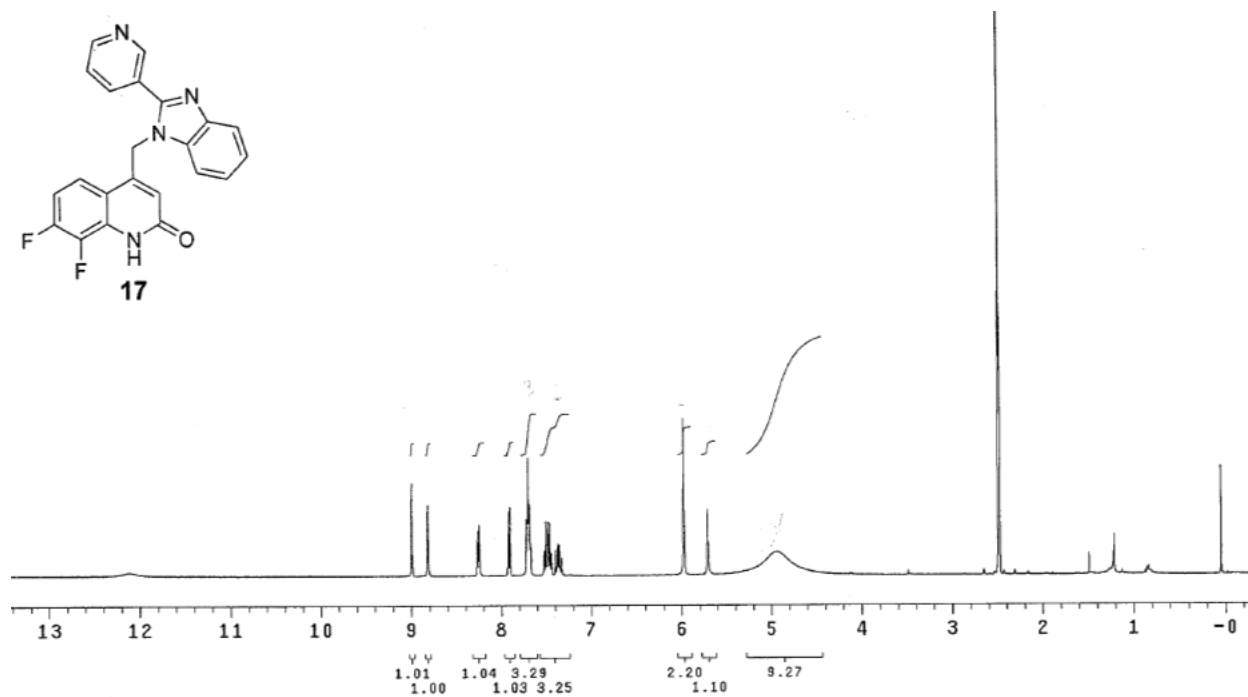
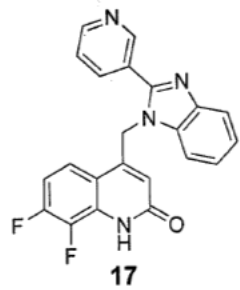
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

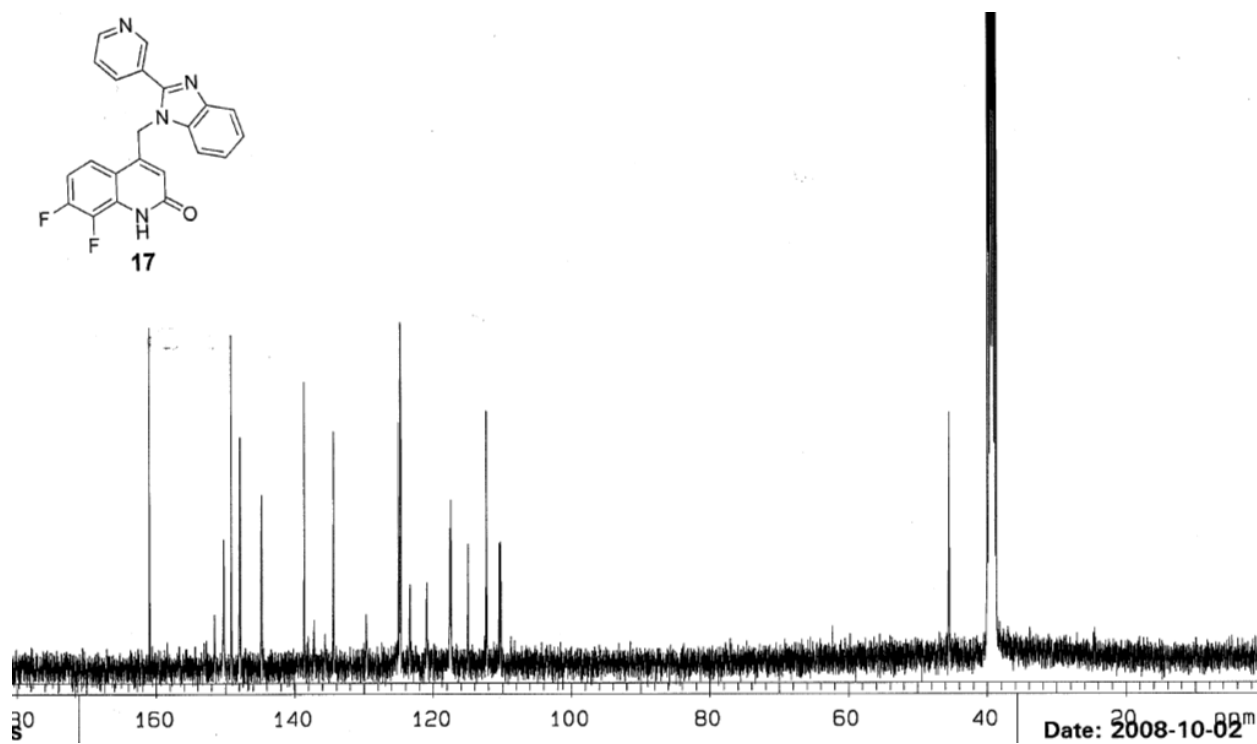
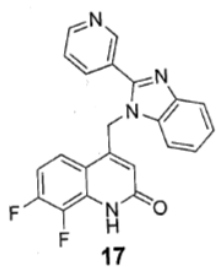
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.531	BB	0.1619	2271.29614	224.78845	94.4537
2	6.237	BB	0.1245	133.36945	16.81492	5.5463

Totals : 2404.66559 241.60337



Compound 17: 7,8-Difluoro-4-((2-(pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one

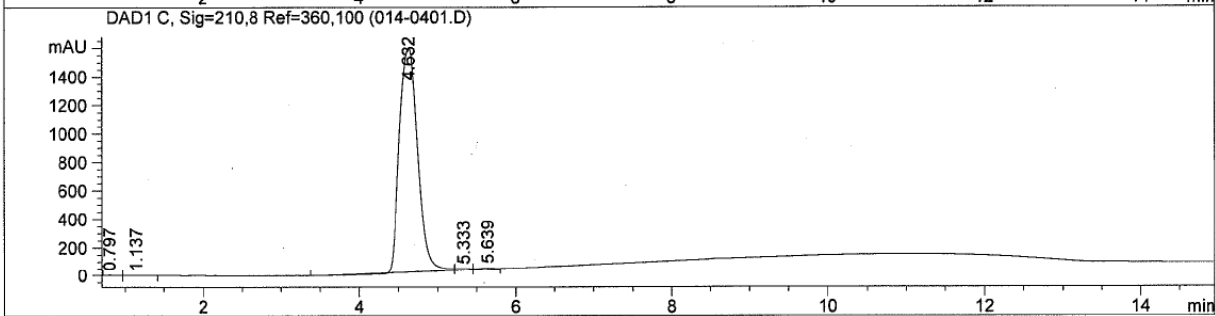
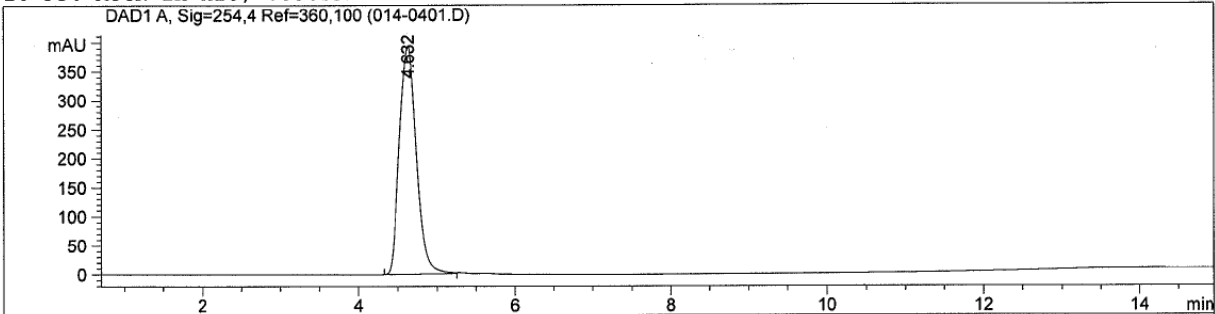




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=====
Injection Date : 11/5/2007 2:32:07 PM      Seq. Line : 4
Sample Name    :                               Location  : Vial 14
Acq. Operator  : 14                          Inj       : 1
Acq. Instrument : Kalypsys                    Inj Volume: 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method        : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/5/2007 1:18:30 PM by 14
1%-95% AcCN in H2O, .05%TFA

```



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Area Percent Report
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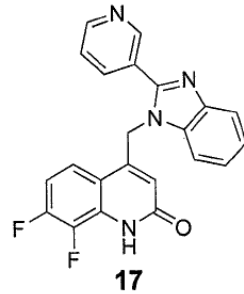
Sorted By      : Signal
Multiplier    : 1.0000
Dilution      : 1.0000
Use Multiplier & Dilution Factor with ISTDs

```

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.632	BB	0.2418	5928.14600	393.41489	100.0000

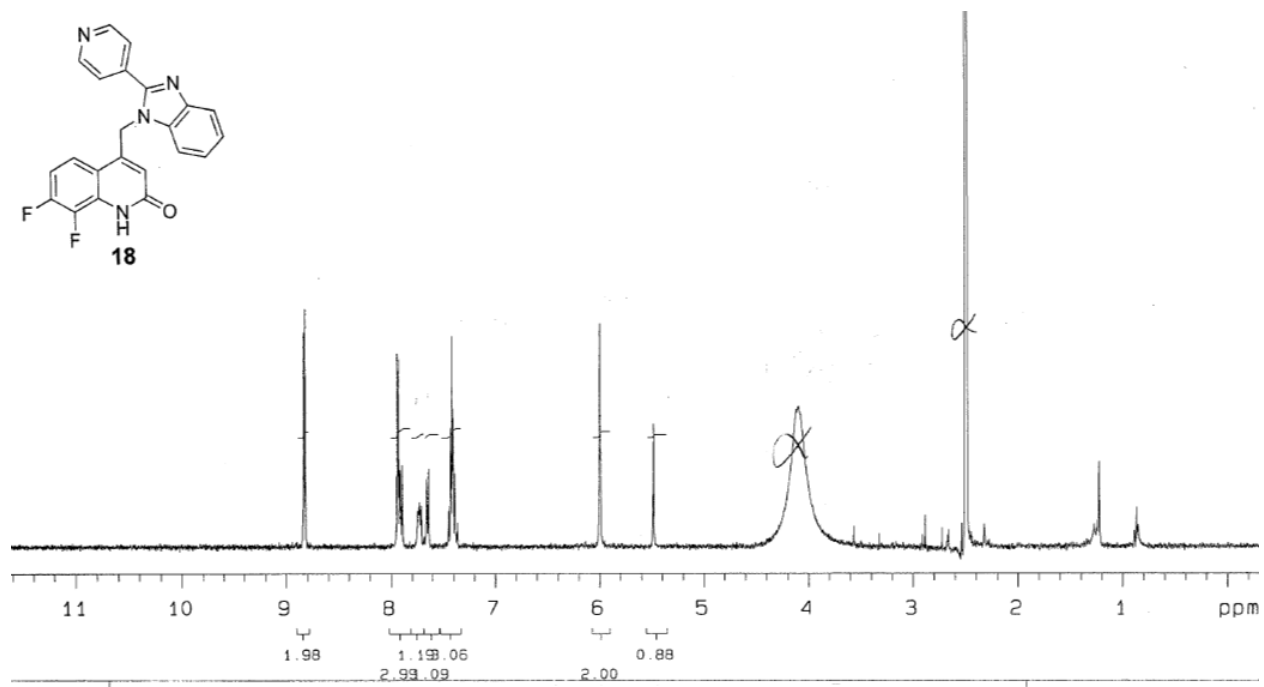
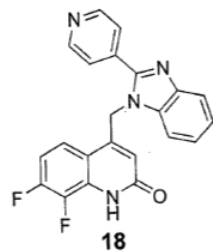
Totals : 5928.14600 393.41489



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.797	BV	0.1116	21.57441	3.08294	0.0838
2	1.137	VB	0.1678	14.96383	1.30464	0.0581
3	4.632	BV	0.2615	2.53615e4	1577.76221	98.5420
4	5.333	VV	0.1818	158.71956	12.87679	0.6167

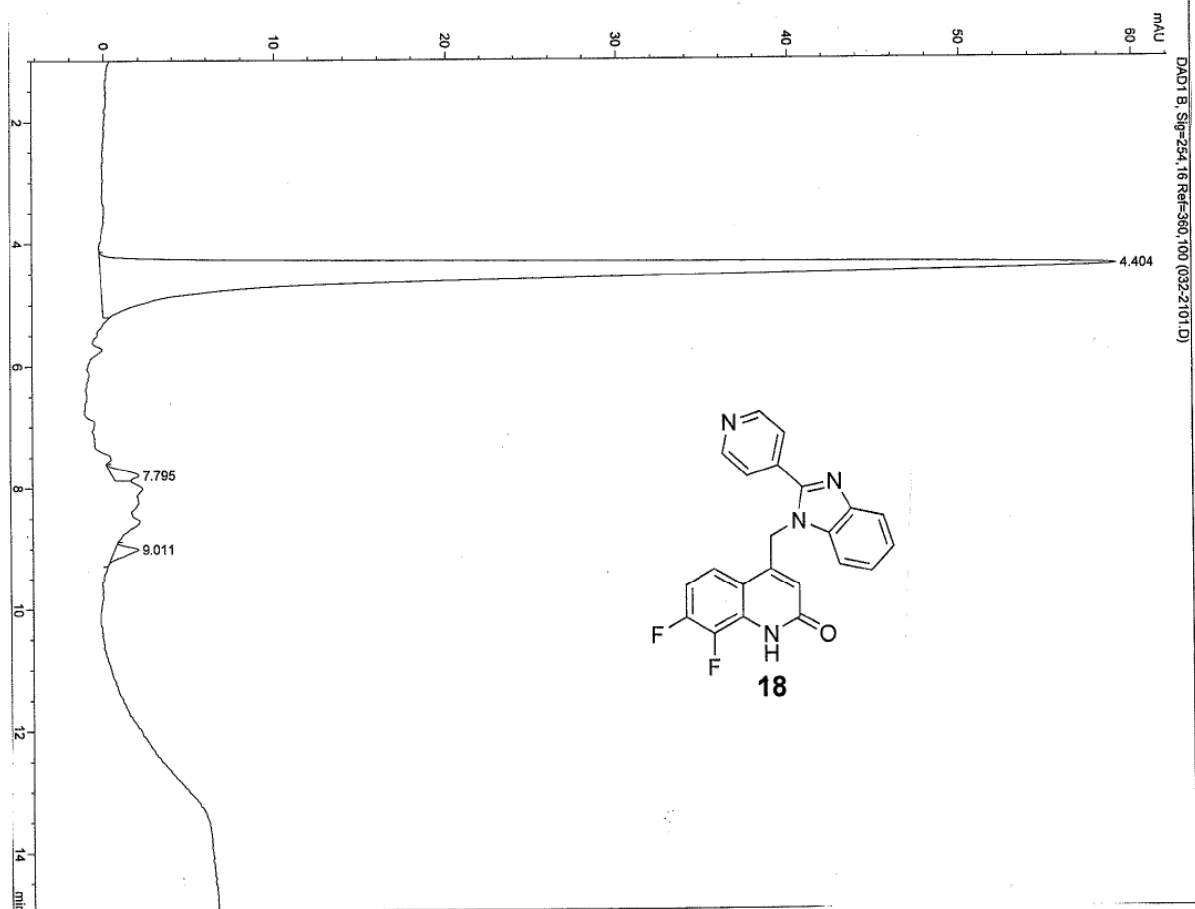
Compound 18: 7,8-Difluoro-4-((2-(pyridin-4-yl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)quinolin-2(1*H*)-one



```

=====
Injection Date : 10/31/2008 2:15:45 PM      Seq. Line : 21
Sample Name   :                               Location  : Vial 32
Acq. Operator : 1                            Inj       : 1
Acq. Instrument : Kalypsys                    Inj Volume: 5 µl
Sequence File : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method        : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed  : 10/31/2008 8:33:04 AM by 1
1%-95% AccN in H2O, .05%TFA
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Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

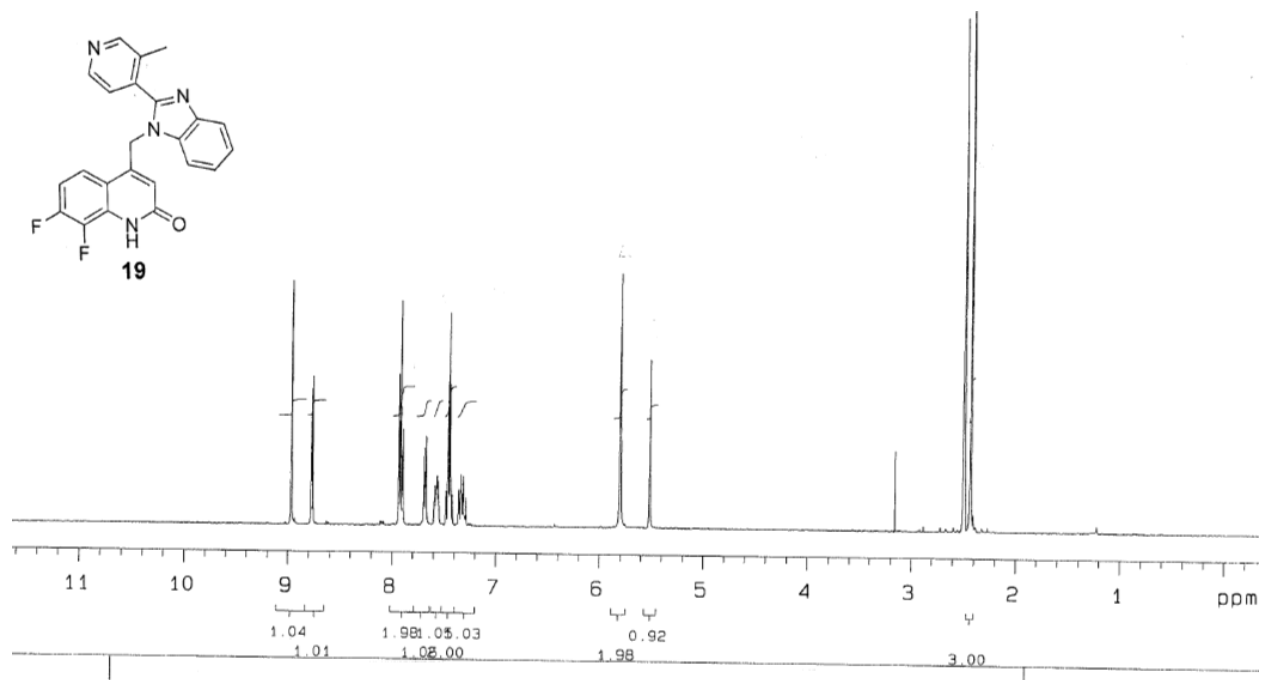
```

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.404	BB	0.2758	1067.16675	59.35764	97.4359
2	7.795	VV	0.1532	14.97317	1.54272	1.3671
3	9.011	BB	0.1331	13.10961	1.37655	1.1970

Totals : 1095.24953 62.27691

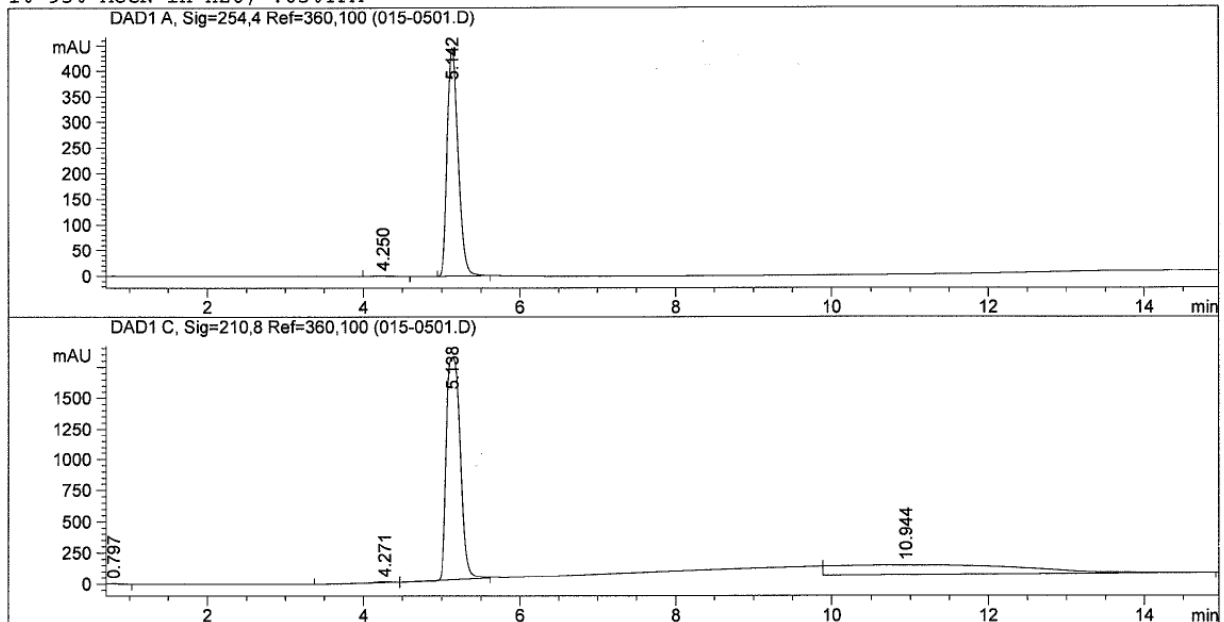
Compound 19: 7,8-Difluoro-4-((2-(3-methylpyridin-4-yl)-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one



```

=====
Injection Date : 11/5/2007 2:49:59 PM      Seq. Line : 5
Sample Name    : F111P00931760           Location  : Vial 15
Acq. Operator  : 14                       Inj      : 1
Acq. Instrument : Kalypsys                 Inj Volume : 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/5/2007 1:18:30 PM by 14
1%-95% AcCN in H2O, .05%TFA

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Area Percent Report
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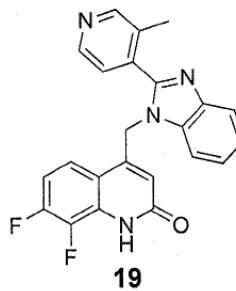
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution      :      1.0000
Use Multiplier & Dilution Factor with ISTDs

```

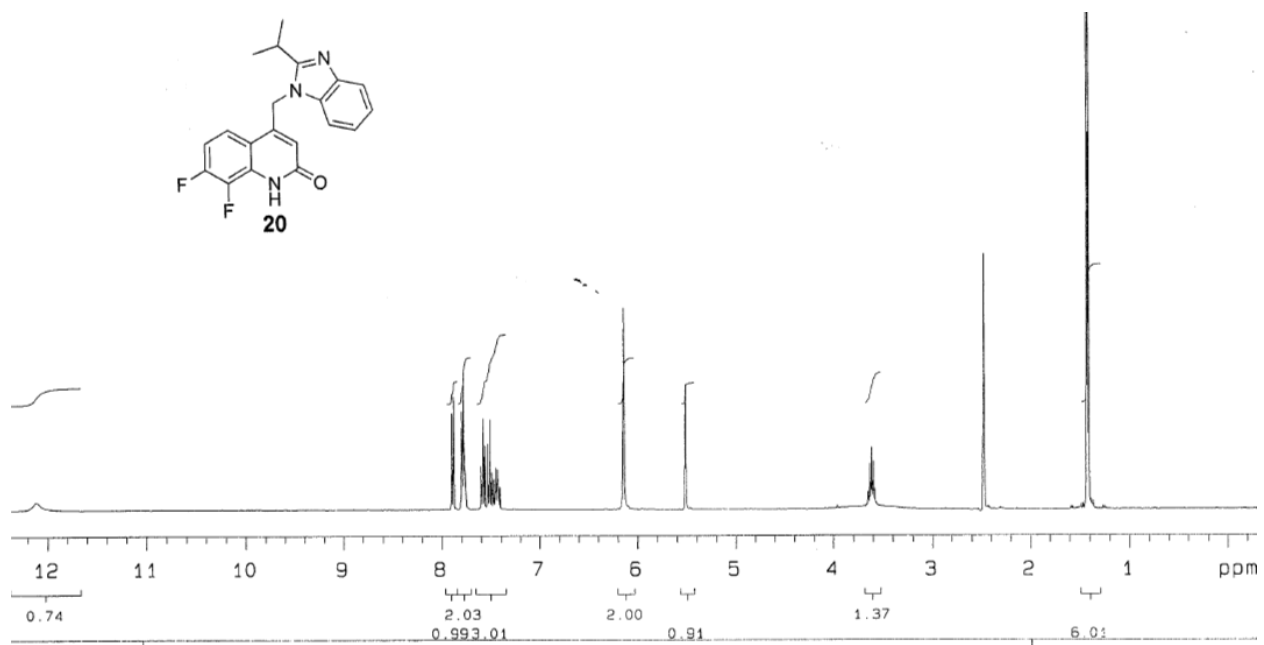
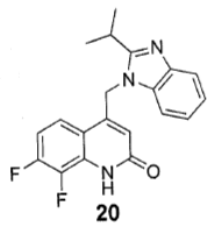
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

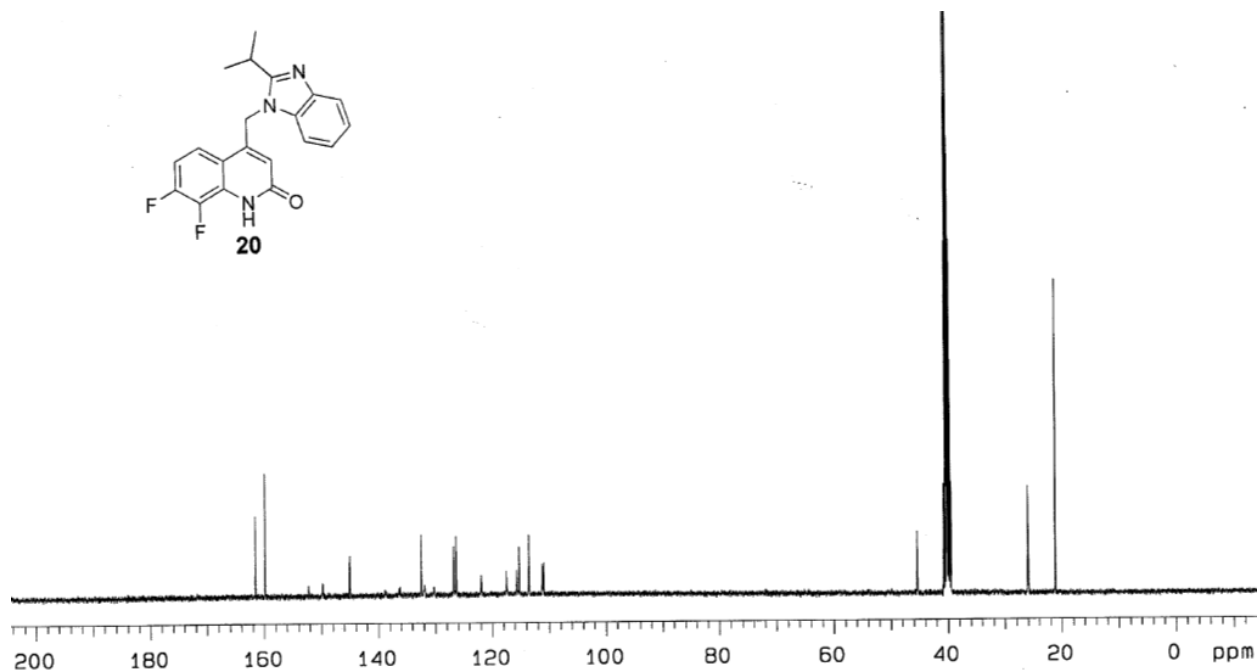
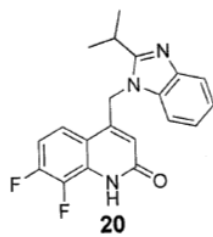
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.250	BB	0.1903	18.21249	1.30880	0.4229
2	5.142	BB	0.1524	4287.88477	445.04013	99.5771

Totals : 4306.09726 446.34893



Compound 20: 7,8-Difluoro-4-((2-isopropyl-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one

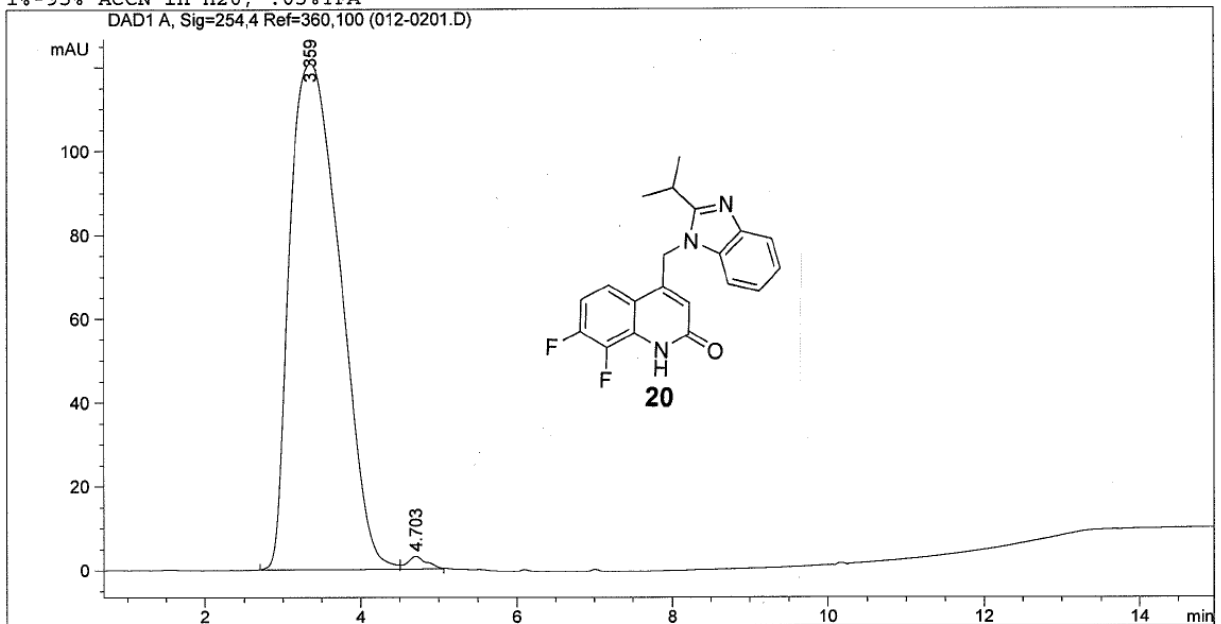




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=====
Injection Date   : 11/1/2007 1:42:22 PM           Seq. Line :    2
Sample Name     :                               Location  : Vial 12
Acq. Operator   : 14                             Inj       :    1
Acq. Instrument : Kalypsys                        Inj Volume: 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 11/1/2007 1:22:57 PM by 14
1%-95% AcCN in H2O, .05%TFA

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Area Percent Report
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Sorted By      :      Signal
Multiplier    :      1.0000
Dilution      :      1.0000
Use Multiplier & Dilution Factor with ISTDs

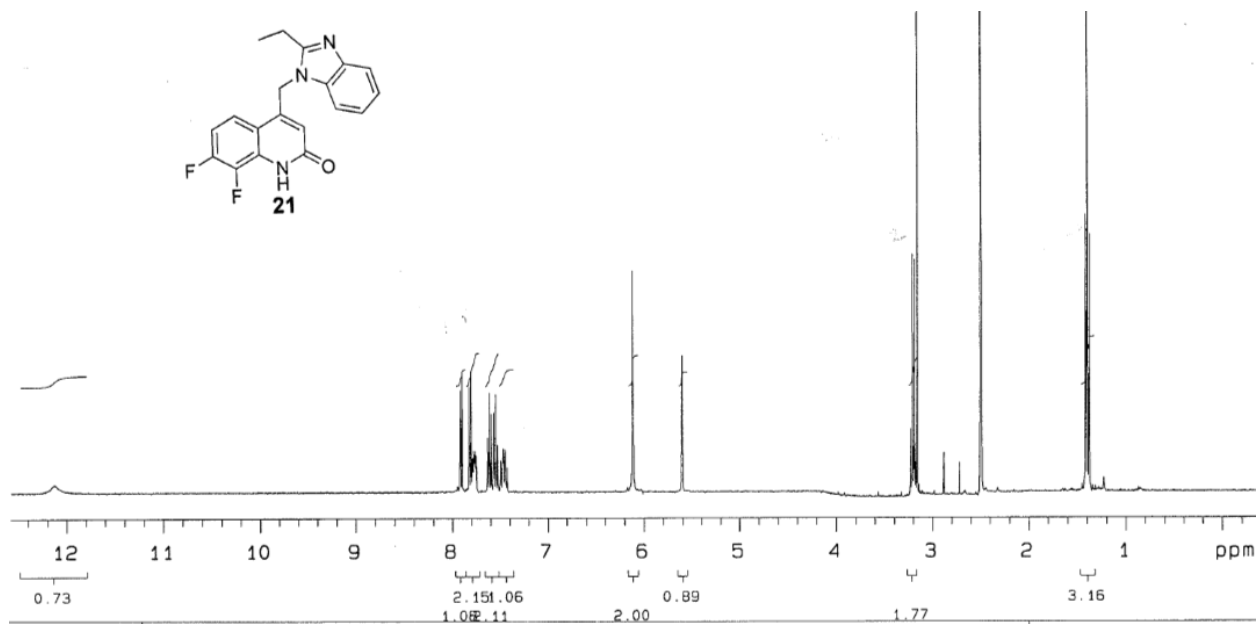
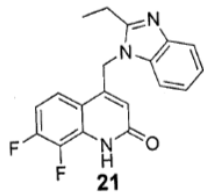
```

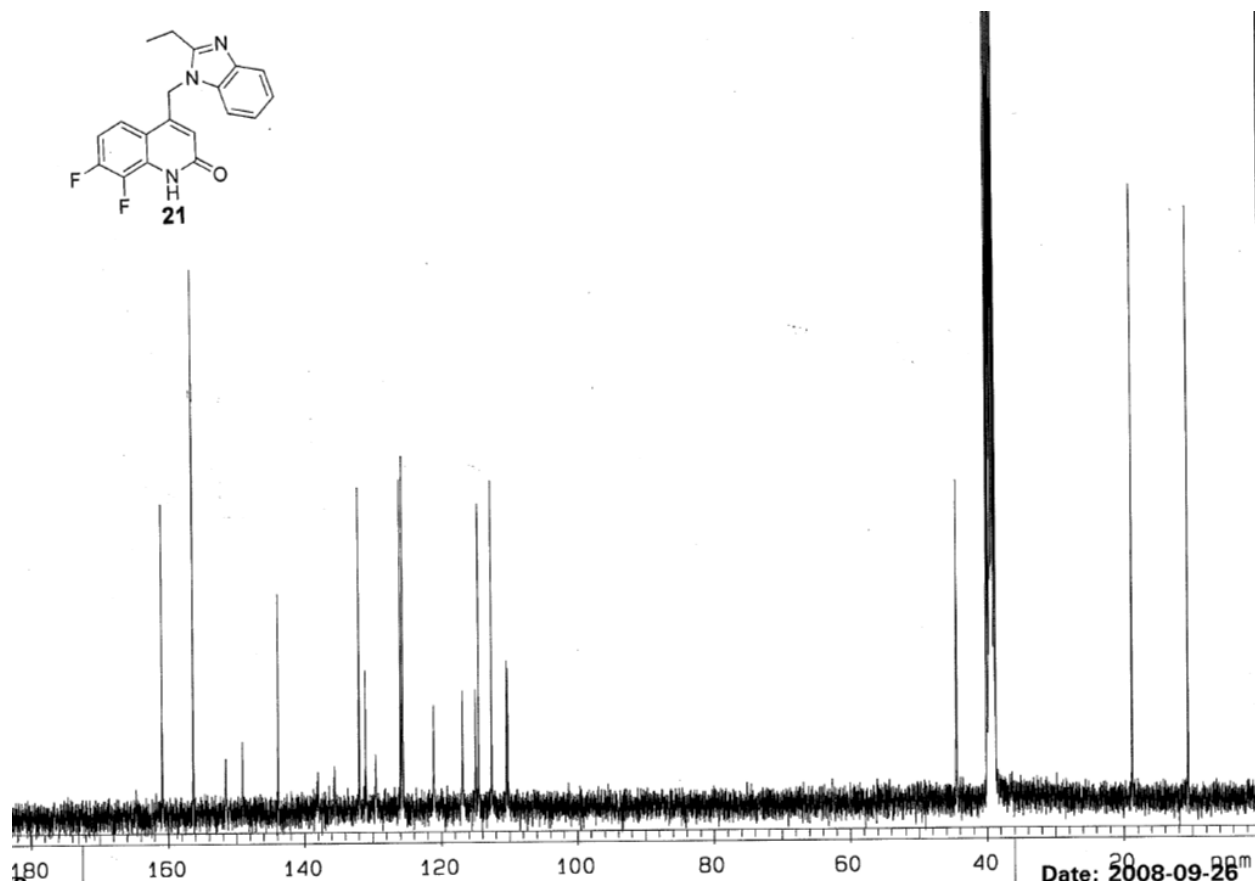
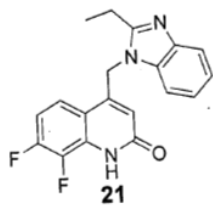
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.359	BV	0.6920	5411.58301	120.49619	99.0657
2	4.703	VB	0.2317	51.03888	3.04245	0.9343

Totals : 5462.62188 123.53864

Compound 21: 7,8-Difluoro-4-((2-ethyl-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one

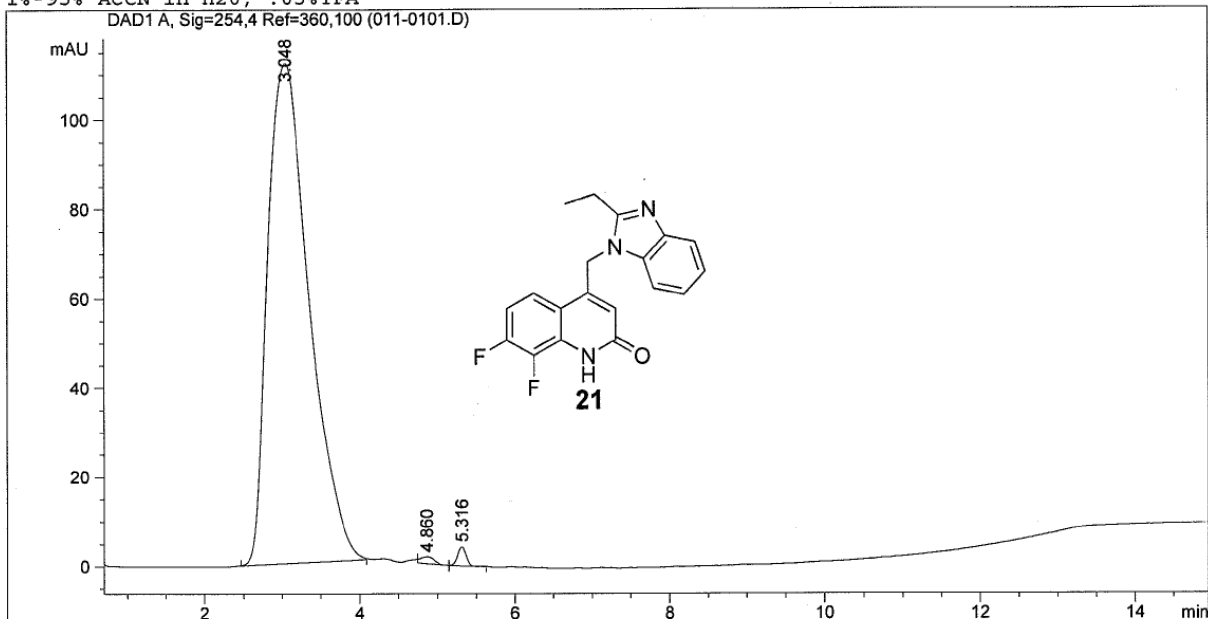




```

=====
Injection Date : 11/1/2007 2:50:45 PM      Seq. Line : 1
Sample Name   :                               Location  : Vial 11
Acq. Operator : 14                          Inj       : 1
Acq. Instrument : Kalypsys                   Inj Volume: 5 µl
Sequence File : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method        : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed  : 11/1/2007 2:49:15 PM by 14
1%-95% AcCN in H2O, .05%TFA

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                          Area Percent Report
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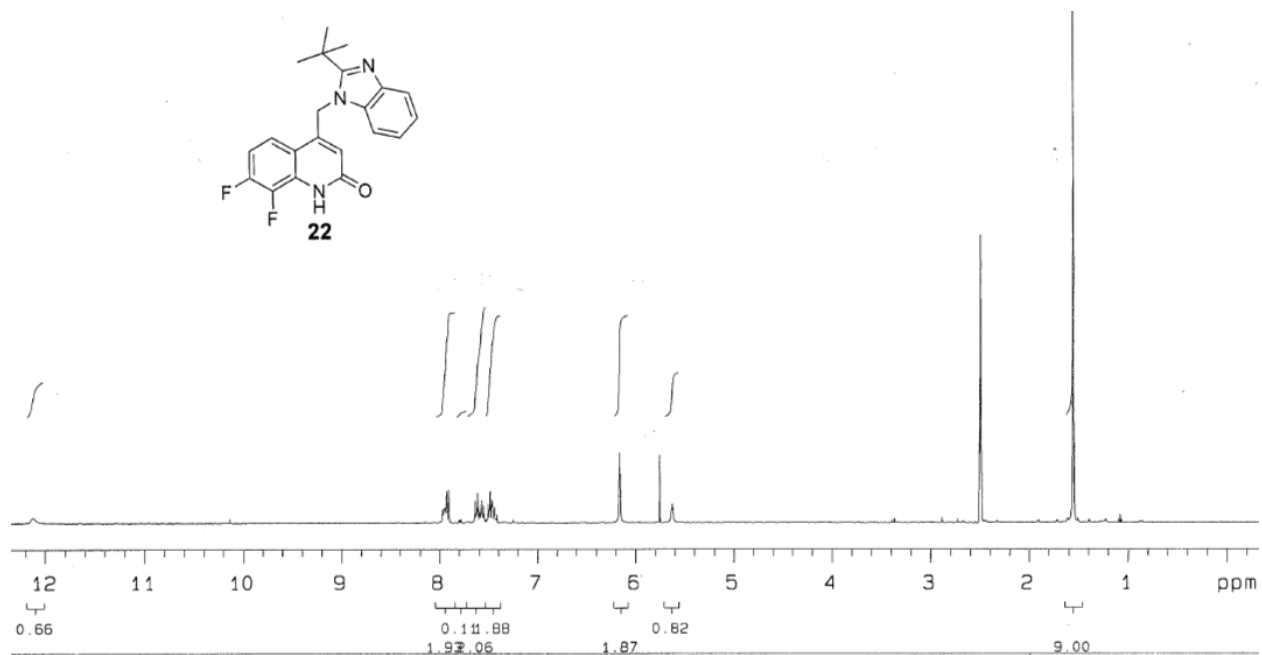
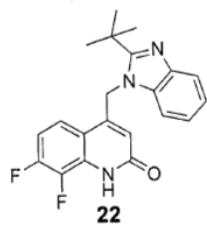
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution      :      1.0000
Use Multiplier & Dilution Factor with ISTDs

```

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.048	BB	0.5806	4168.82080	111.91585	98.8049
2	4.860	BV	0.1800	18.02817	1.50219	0.4273
3	5.316	VB	0.1201	32.39688	4.19616	0.7678

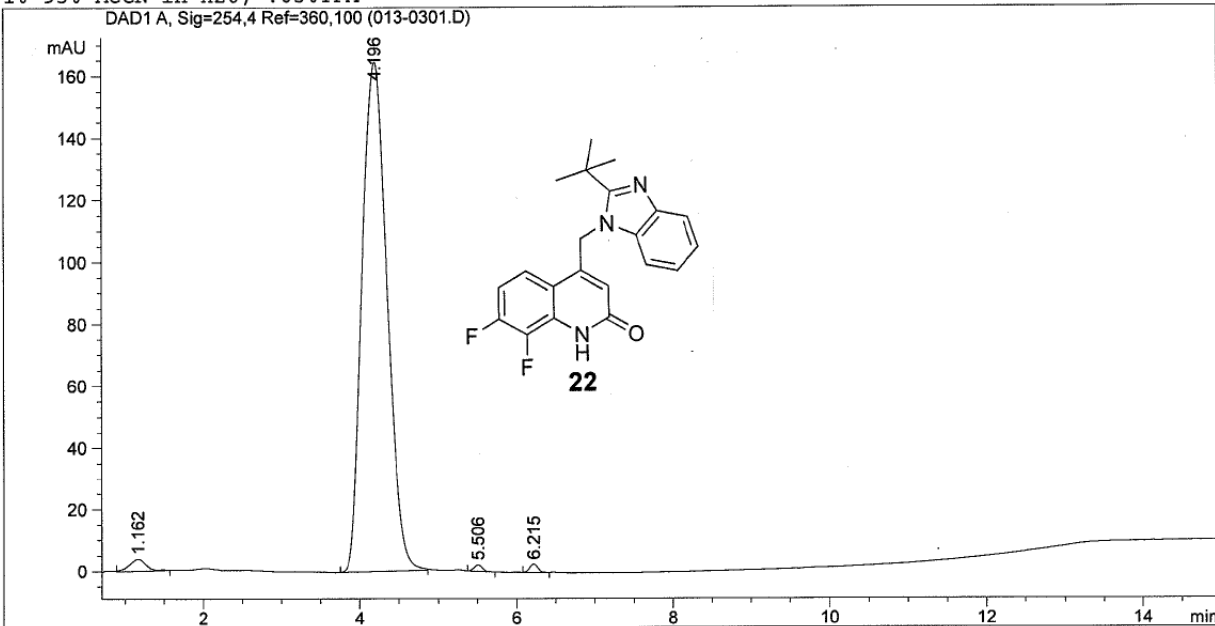
Compound 22: 4-((2-*tert*-Butyl-1*H*-benzo[*d*]imidazol-1-yl)methyl)-7,8-difluoroquinolin-2(1*H*)-one



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=====
Injection Date   : 11/1/2007 3:26:27 PM           Seq. Line :    3
Sample Name     :                               Location  : Vial 13
Acq. Operator   : 14                             Inj       :    1
Acq. Instrument : Kalypsys                        Inj Volume: 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 11/1/2007 2:49:15 PM by 14
1%-95% AcCN in H2O, .05%TFA

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Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

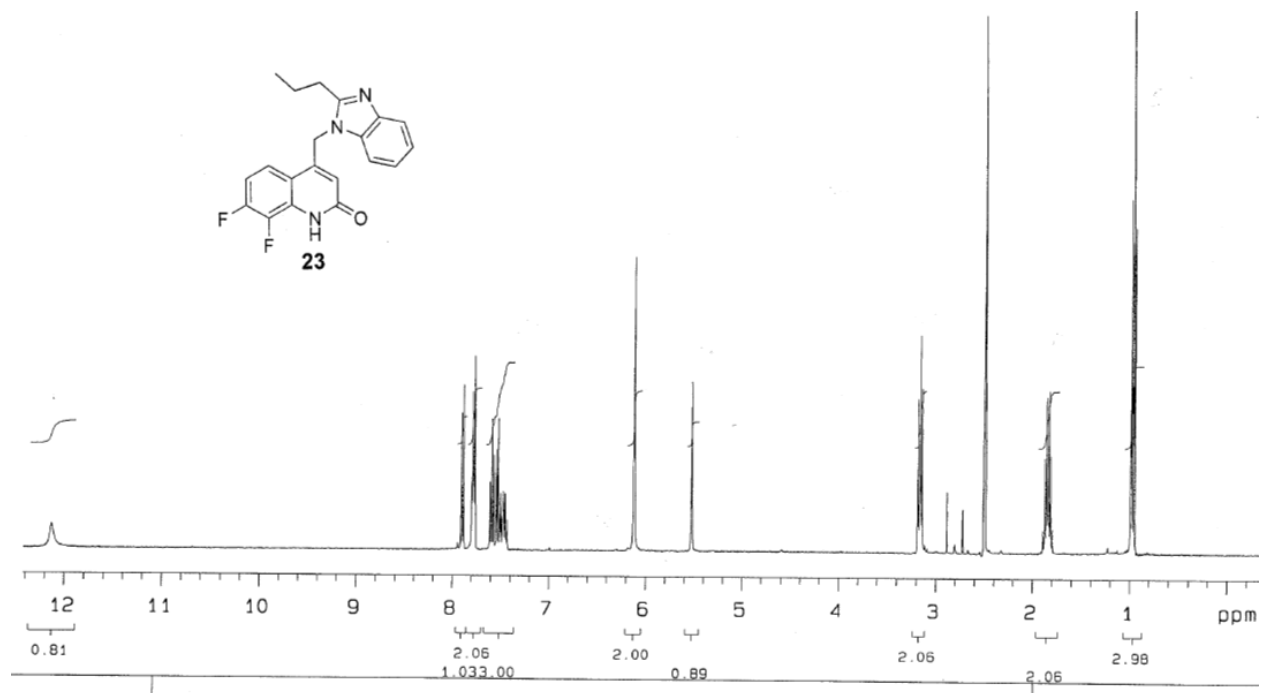
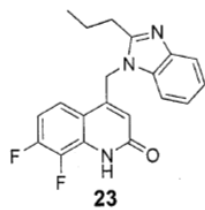
```

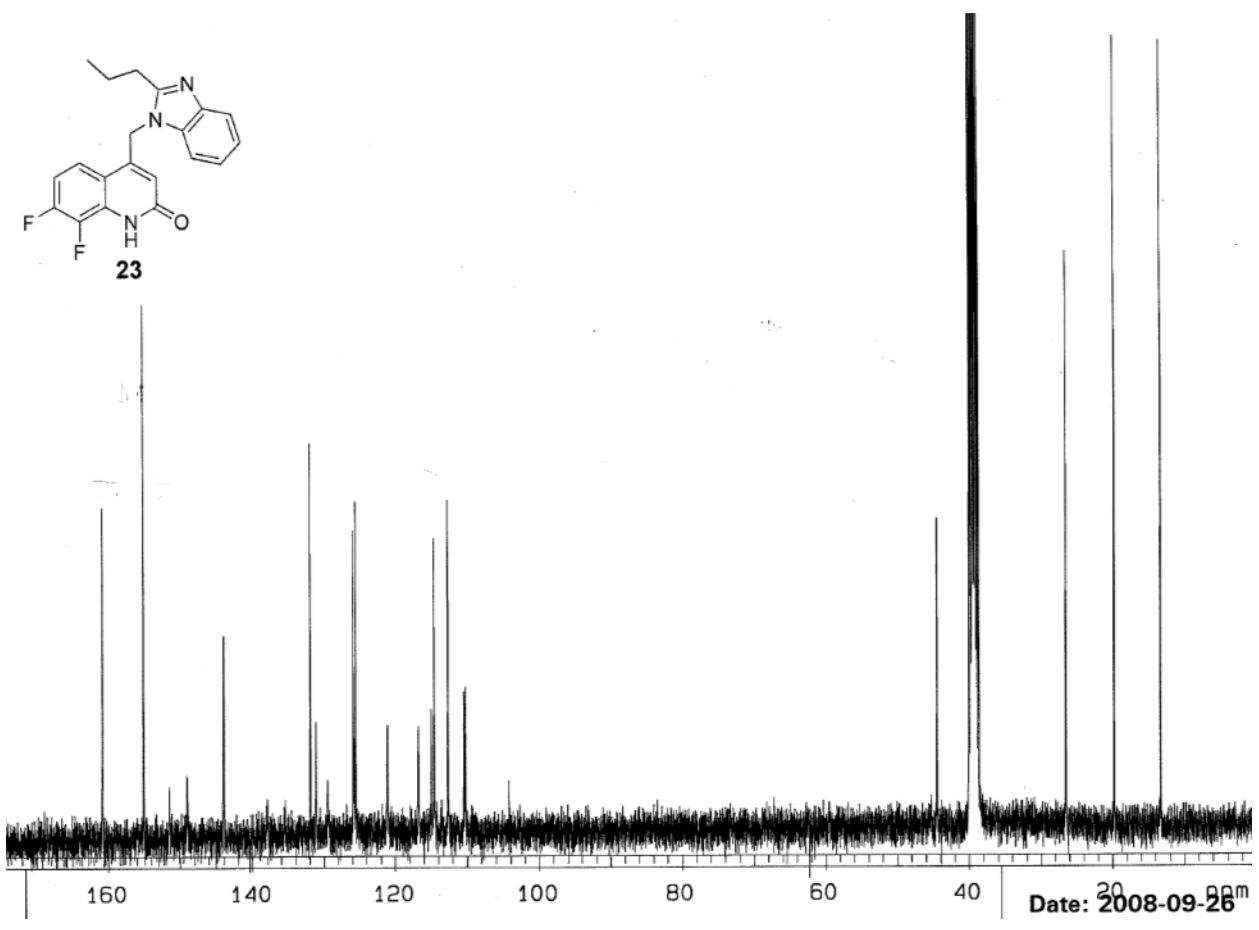
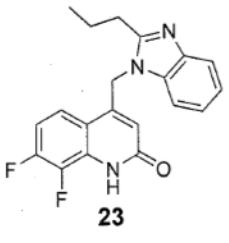
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.162	BB	0.2235	57.07073	3.83837	1.5358
2	4.196	BB	0.3571	3625.61328	164.49355	97.5683
3	5.506	BB	0.1164	14.24533	1.96944	0.3834
4	6.215	BB	0.1140	19.04382	2.64466	0.5125

Totals : 3715.97316 172.94602

Compound 23: 7,8-Difluoro-4-((2-propyl-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one

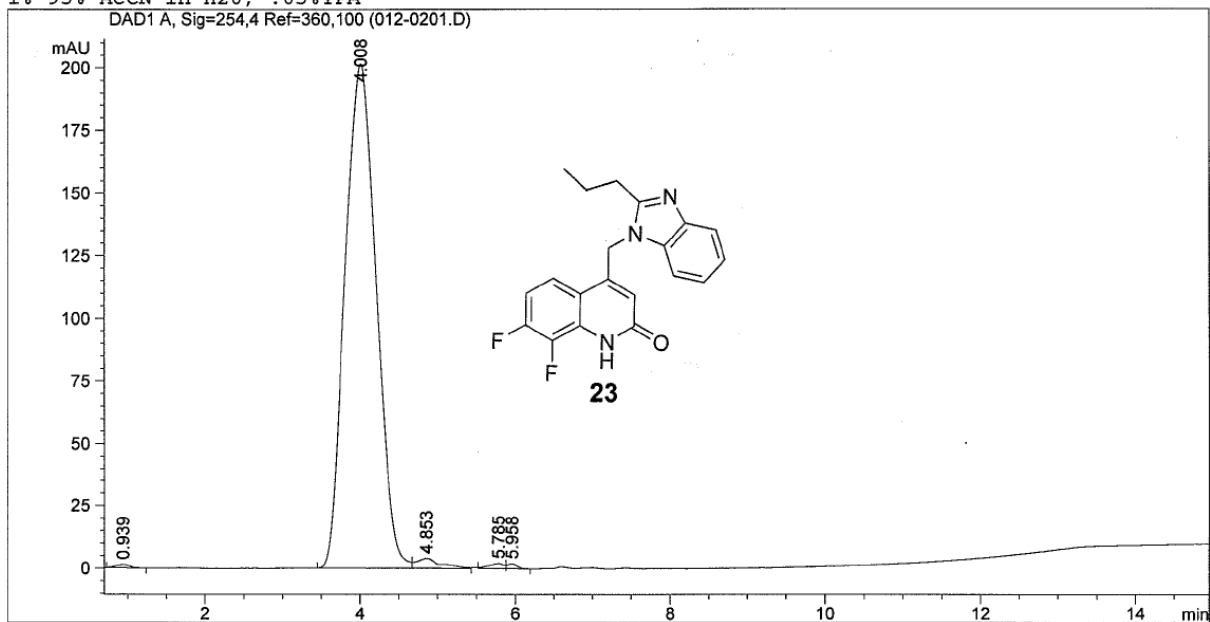




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=====
Injection Date   : 11/1/2007 3:08:39 PM           Seq. Line :    2
Sample Name     :                               Location  : Vial 12
Acq. Operator  : 14                             Inj       :    1
Acq. Instrument : Kalypsys                       Inj Volume: 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/1/2007 2:49:15 PM by 14
1%-95% AcCN in H2O, .05%TFA

```



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                          Area Percent Report
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Sorted By           :      Signal
Multiplier          :      1.0000
Dilution           :      1.0000
Use Multiplier & Dilution Factor with ISTDs

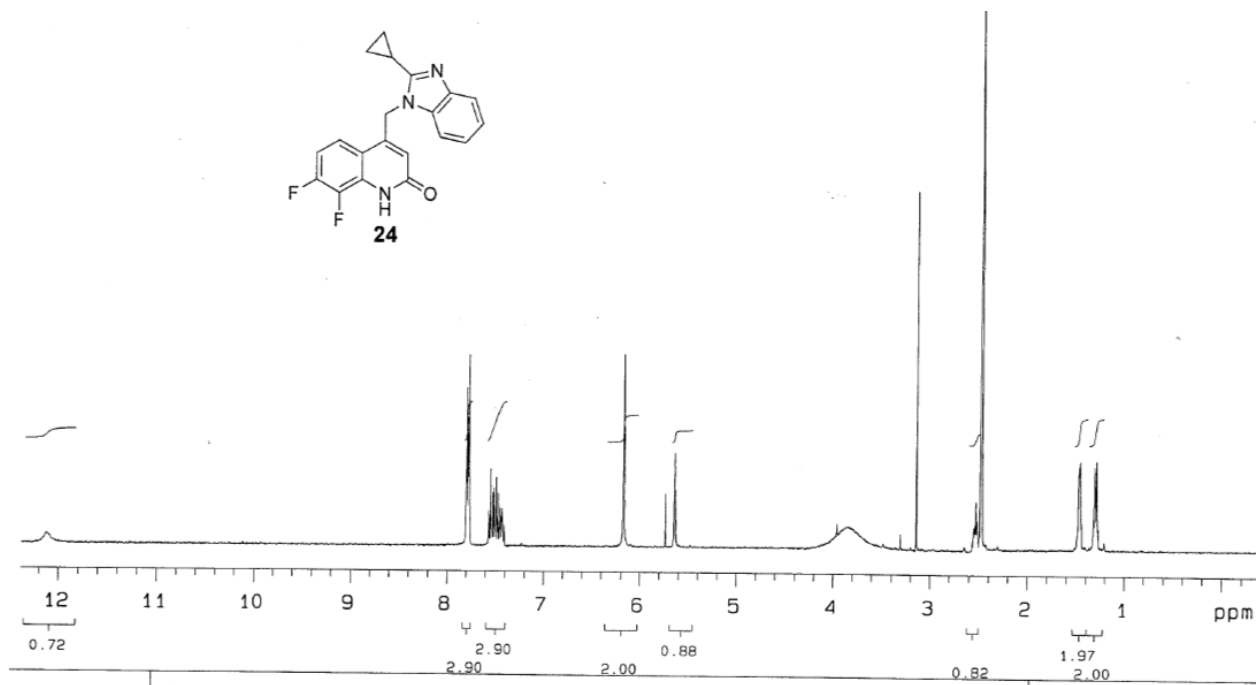
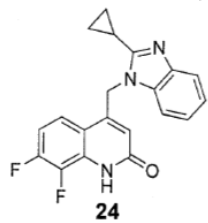
```

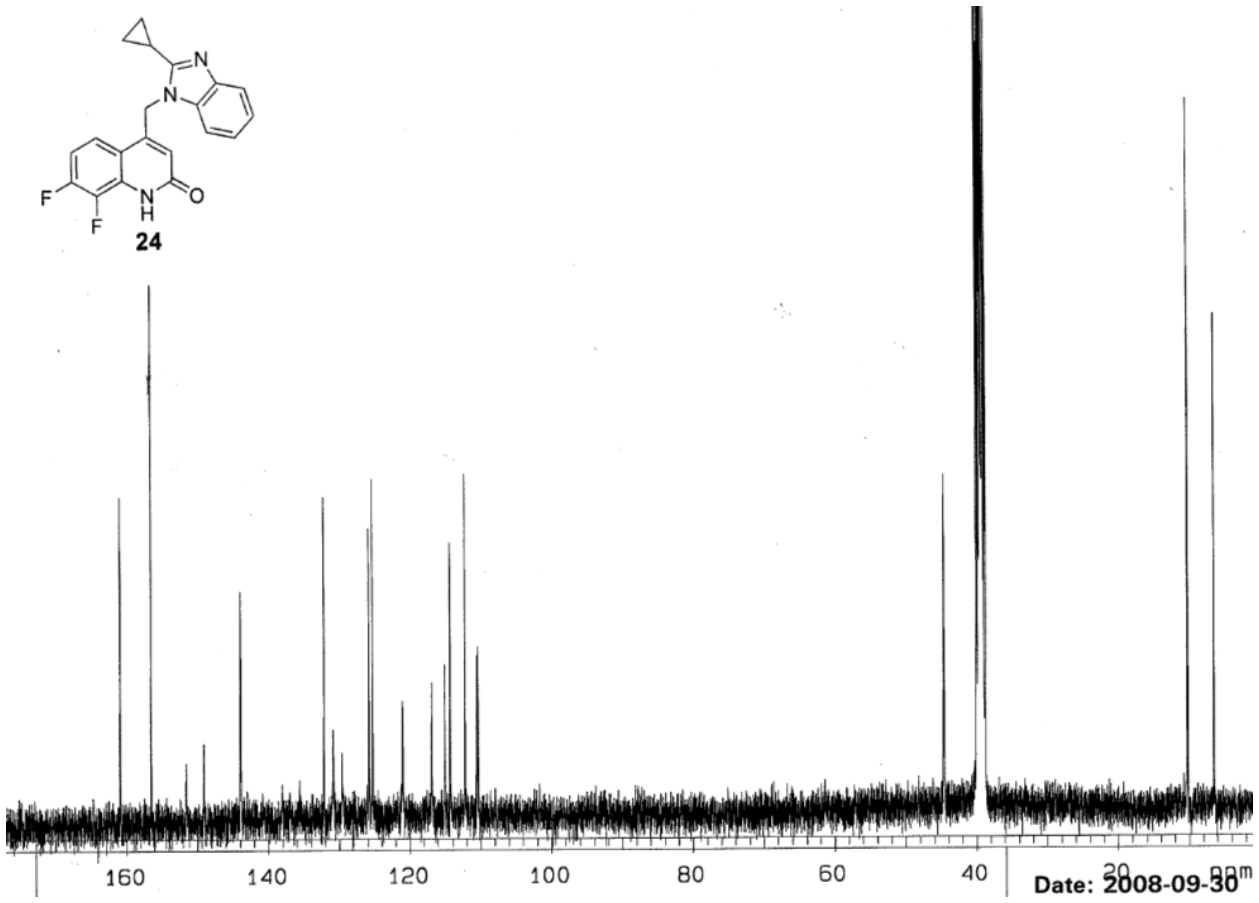
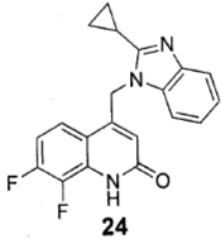
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.939	BB	0.1650	14.88026	1.34609	0.2584
2	4.008	BV	0.4527	5610.06738	201.59886	97.4242
3	4.853	VB	0.3026	88.69143	4.00093	1.5402
4	5.785	BV	0.1879	28.13593	2.07901	0.4886
5	5.958	VB	0.1284	16.61691	1.97070	0.2886

```
Totals :                5758.39191  210.99559
```

Compound 24: 4-((2-Cyclopropyl-1H-benzo[d]imidazol-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-one

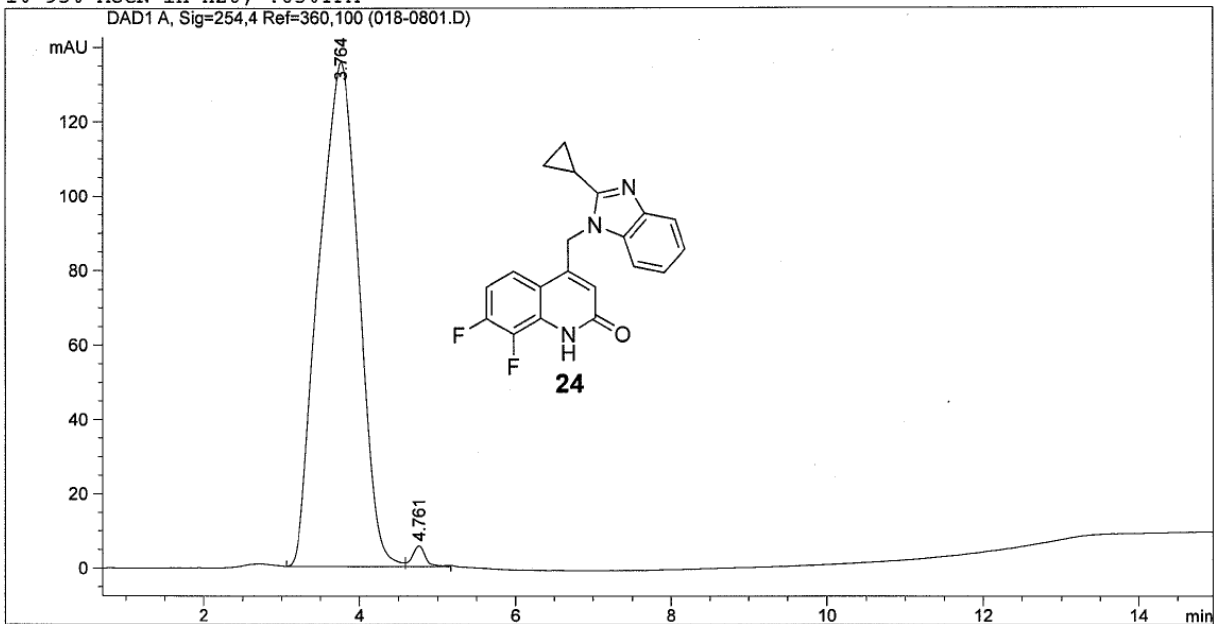




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=====
Injection Date   : 11/1/2007 4:55:10 PM           Seq. Line   :    8
Sample Name     :                               Location    : Vial 18
Acq. Operator   :                               Inj         :    1
Acq. Instrument : Kalypsys                       Inj Volume  : 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 11/1/2007 2:49:15 PM by 14
1%-95% AcCN in H2O, .05%TFA

```



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Area Percent Report
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Sorted By       :      Signal
Multiplier      :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

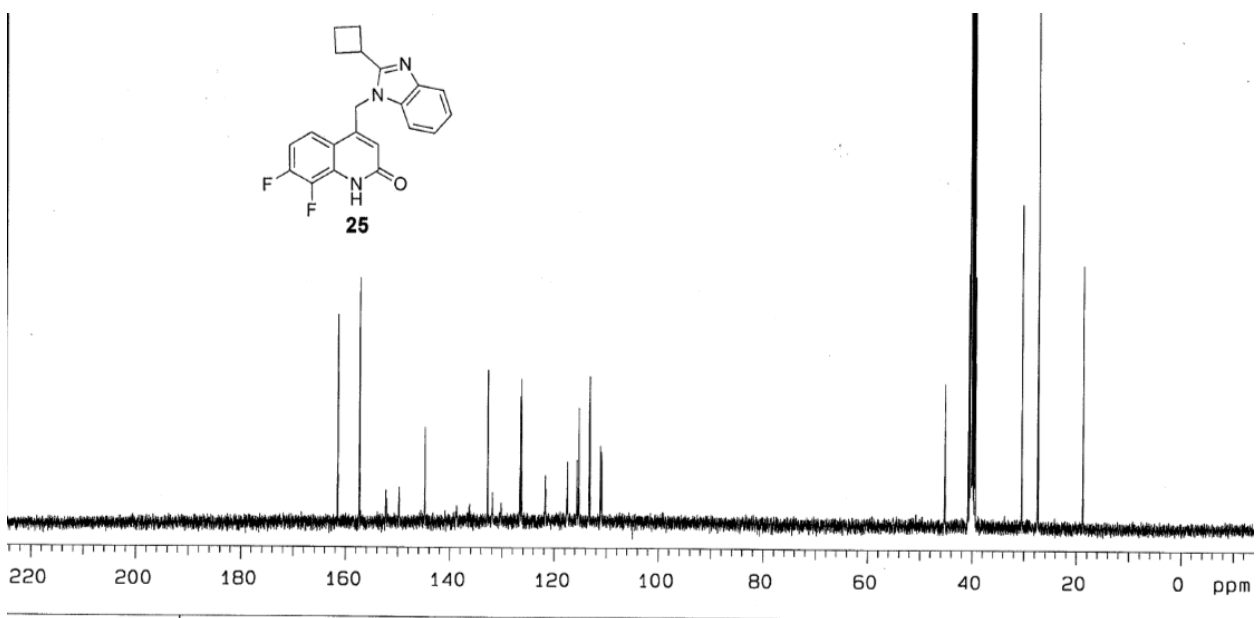
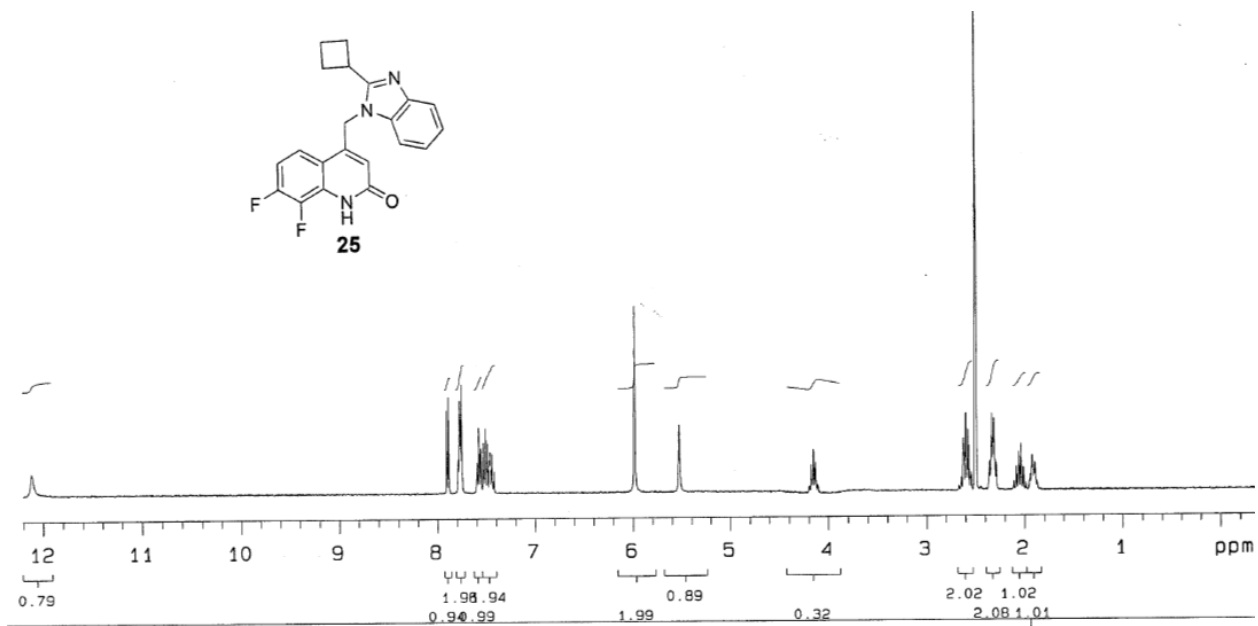
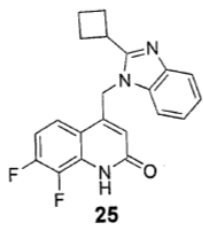
```

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.764	BV	0.5711	4818.09082	135.42969	98.6806
2	4.761	VB	0.1786	64.41814	5.50320	1.3194

Totals : 4882.50896 140.93288

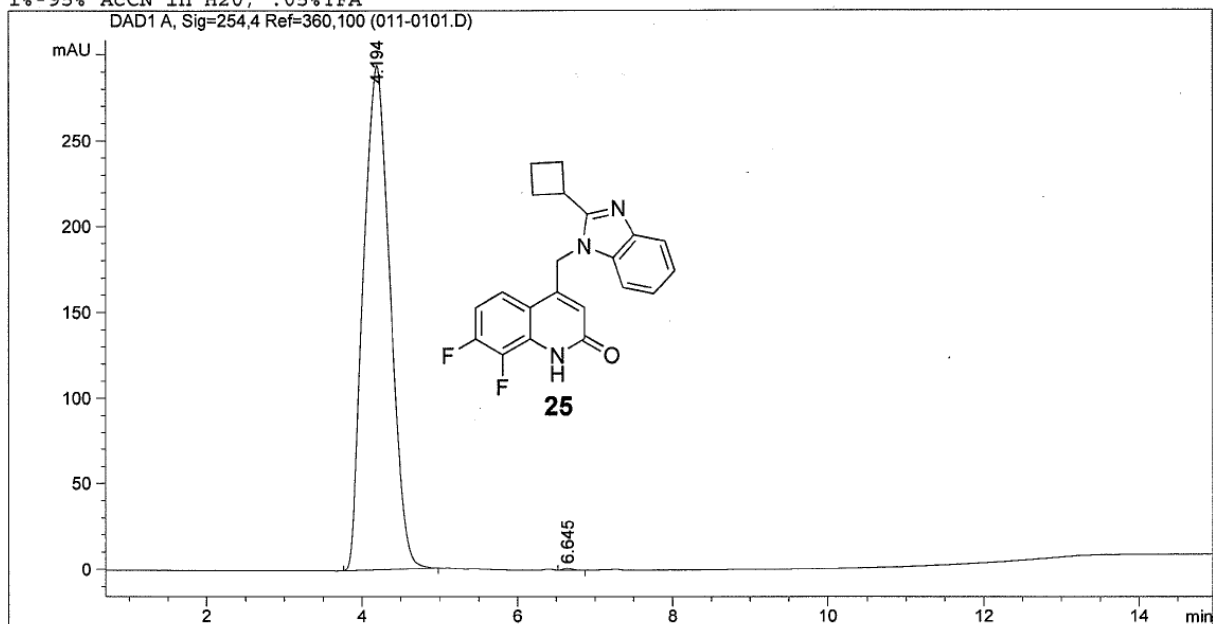
Compound 25: 4-((2-Cyclobutyl-1H-benzo[d]imidazol-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



```

=====
Injection Date   : 11/1/2007 1:24:32 PM           Seq. Line :    1
Sample Name     :                               Location  : Vial 11
Acq. Operator   :                               Inj       :    1
Acq. Instrument : Karyo                          Inj Volume: 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 11/1/2007 1:22:57 PM by 14
1%-95% AcCN in H2O, .05%TFA

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Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

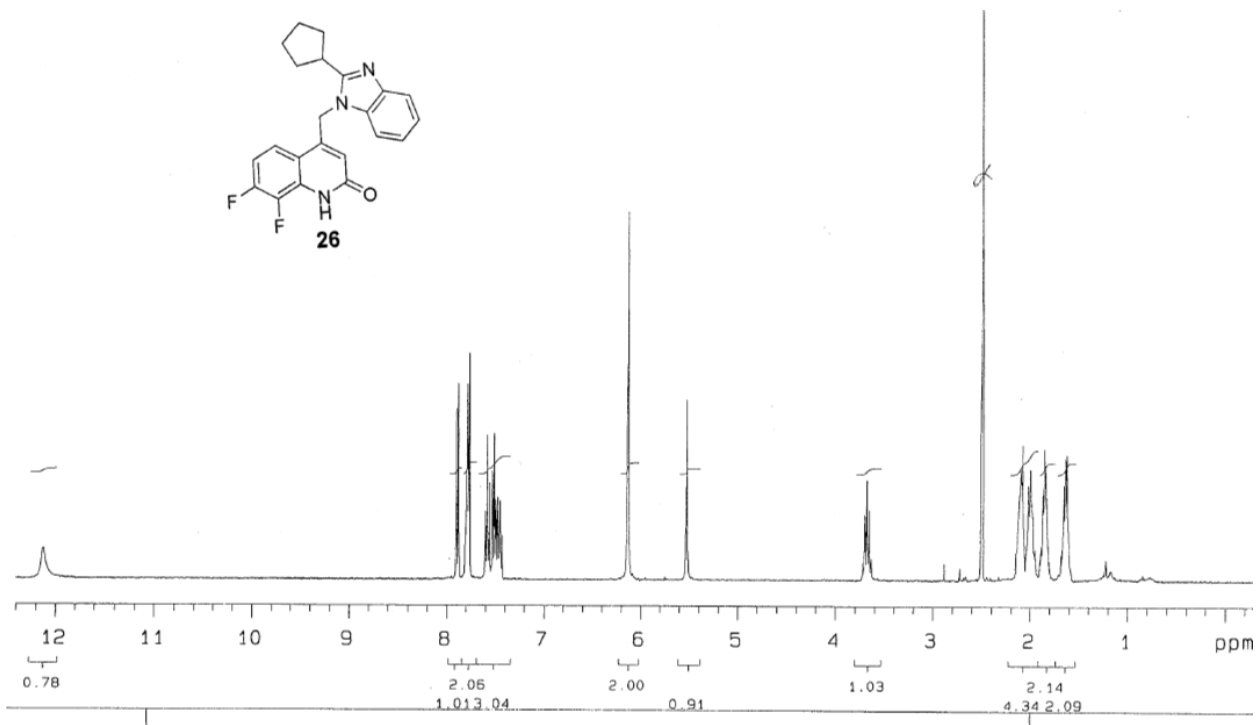
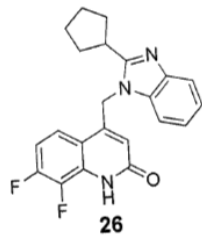
```

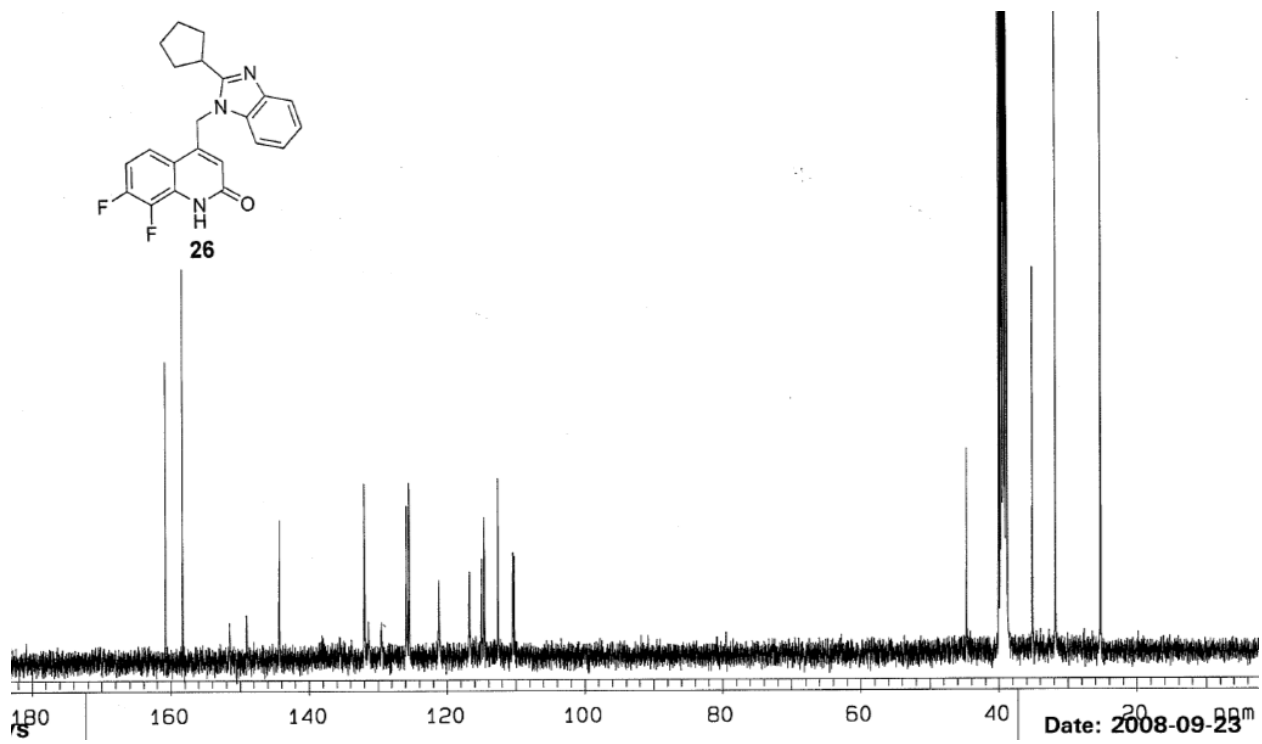
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.194	BB	0.3924	6968.03516	294.07431	99.8602
2	6.645	VB	0.1205	9.75574	1.31601	0.1398

Totals : 6977.79090 295.39032

Compound 26: 4-((2-Cyclopentyl-1H-benzo[d]imidazol-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-one

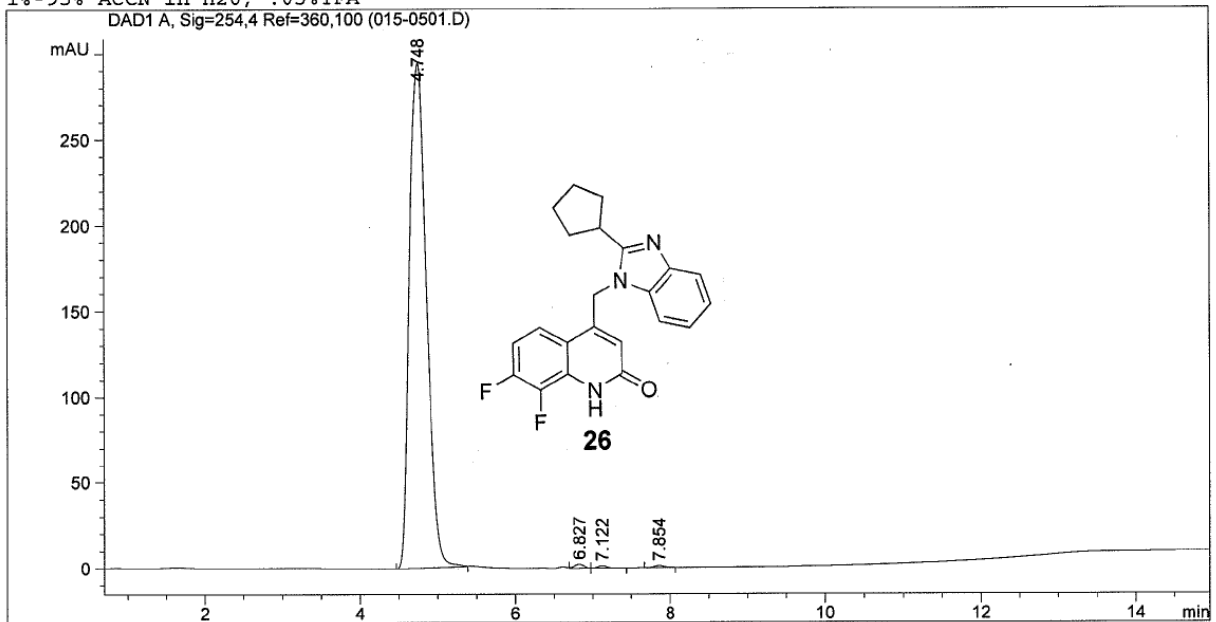




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=====
Injection Date   : 11/1/2007 4:01:59 PM      Seq. Line   :    5
Sample Name     :                          Location    : Vial 15
Acq. Operator  : 14                          Inj         :    1
Acq. Instrument : Kalypsys                    Inj Volume  : 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 11/1/2007 2:49:15 PM by 14
1%-95% AcCN in H2O, .05%TFA

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Area Percent Report
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Sorted By       :      Signal
Multiplier      :      1.0000
Dilution        :      1.0000
Use Multiplier & Dilution Factor with ISTDs

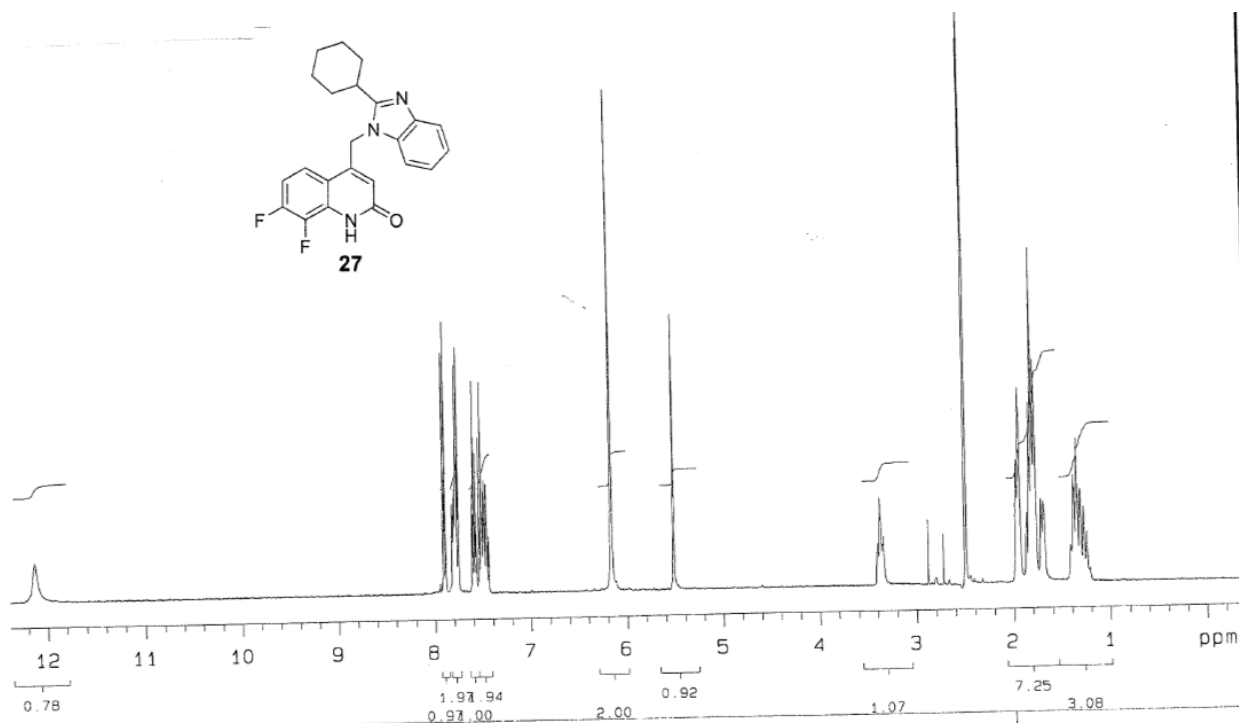
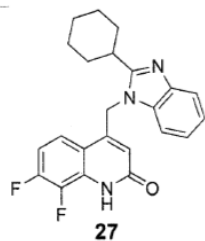
```

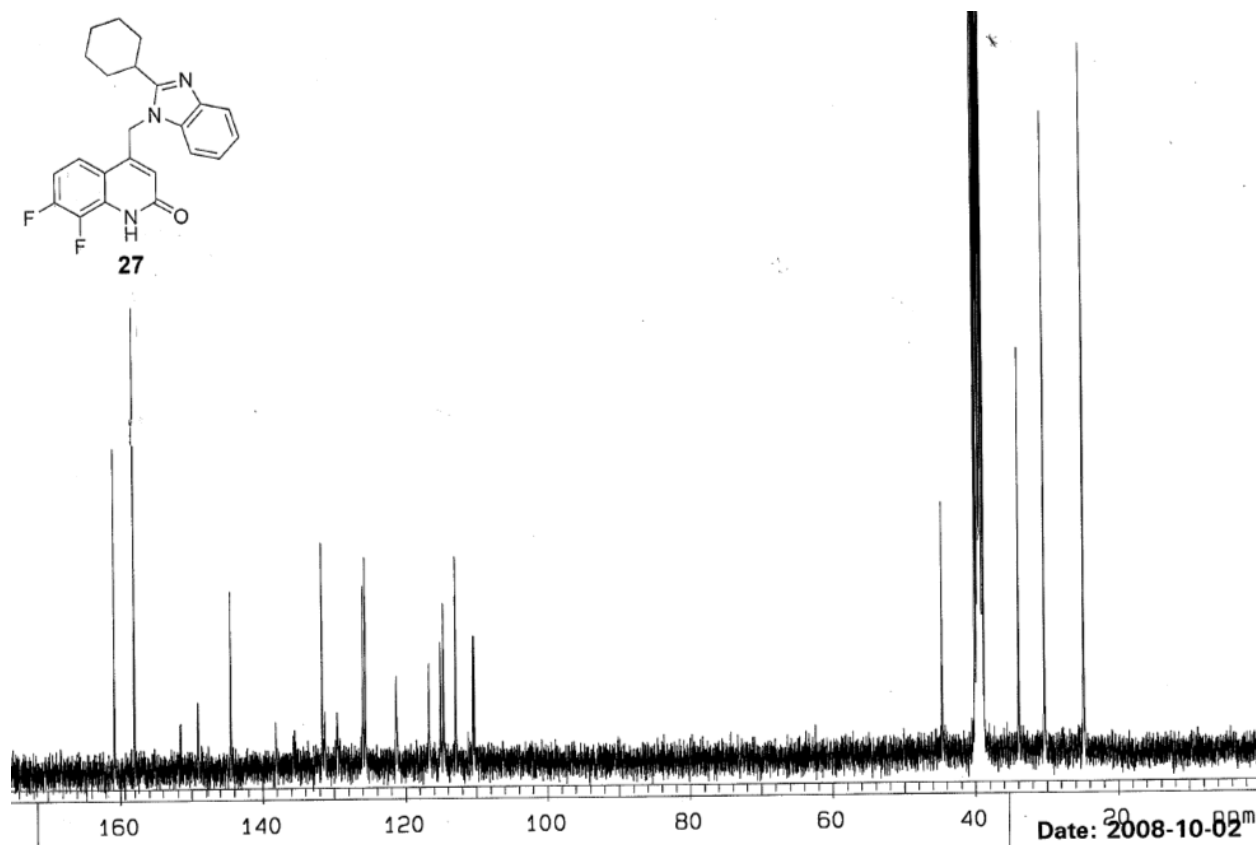
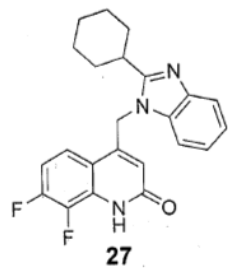
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.748	BB	0.2400	4489.23047	294.28802	99.0408
2	6.827	VV	0.1376	20.26714	2.32684	0.4471
3	7.122	VB	0.1292	11.81071	1.41719	0.2606
4	7.854	BB	0.1448	11.40054	1.17921	0.2515

Totals : 4532.70886 299.21127

Compound 27: 4-((2-Cyclohexyl-1H-benzo[d]imidazol-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-one

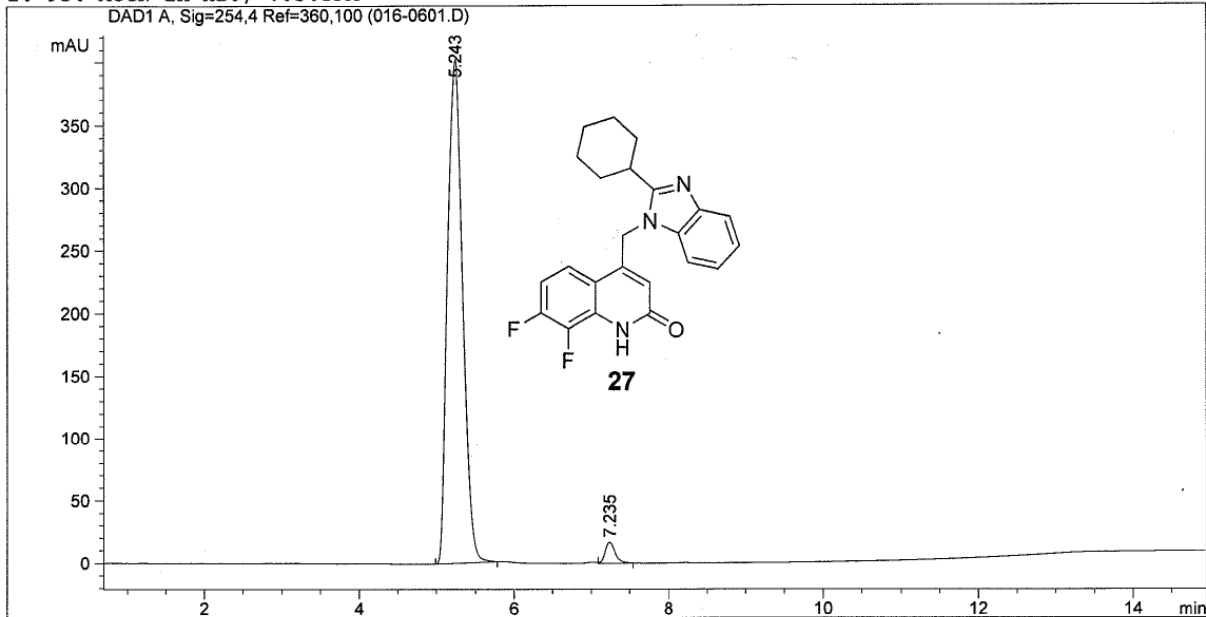




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=====
Injection Date : 11/1/2007 4:19:43 PM      Seq. Line : 6
Sample Name    :                            Location  : Vial 16
Acq. Operator  : --                        Inj       : 1
Acq. Instrument : Kalypsys                  Inj Volume: 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/1/2007 2:49:15 PM by 14
1%-95% AcCN in H2O, .05%TFA

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                          Area Percent Report
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Sorted By      :      Signal
Multiplier    :      1.0000
Dilution      :      1.0000
Use Multiplier & Dilution Factor with ISTDs

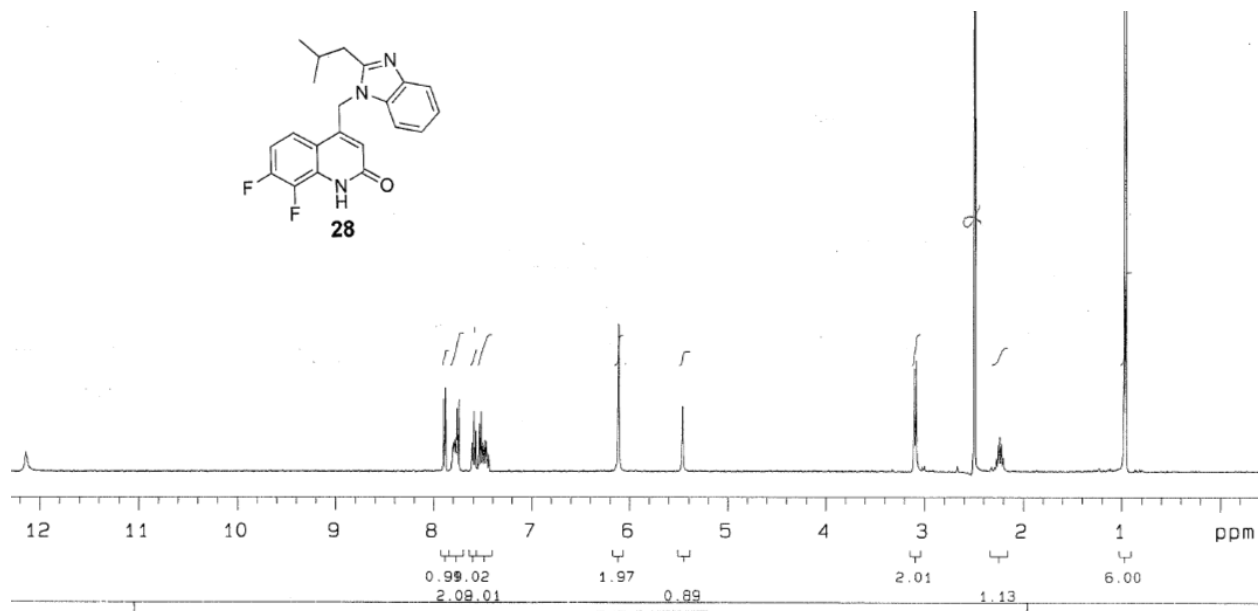
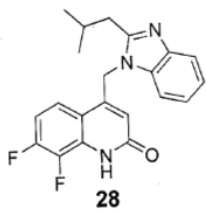
```

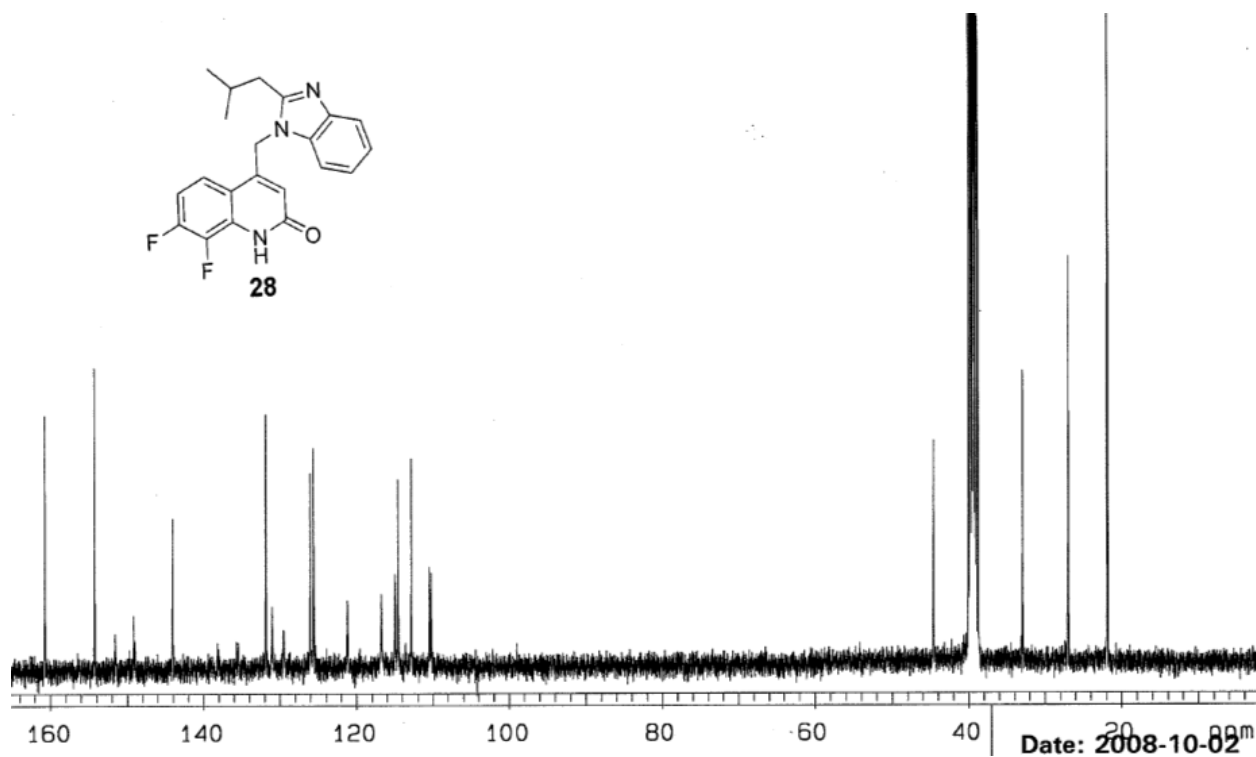
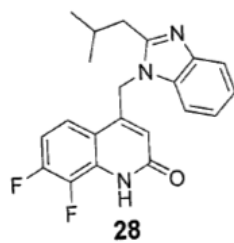
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.243	BB	0.2153	5420.71631	401.94510	97.3261
2	7.235	VB	0.1385	148.92938	16.63371	2.6739

Totals : 5569.64569 418.57881

Compound 28: 7,8-Difluoro-4-((2-isobutyl-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one

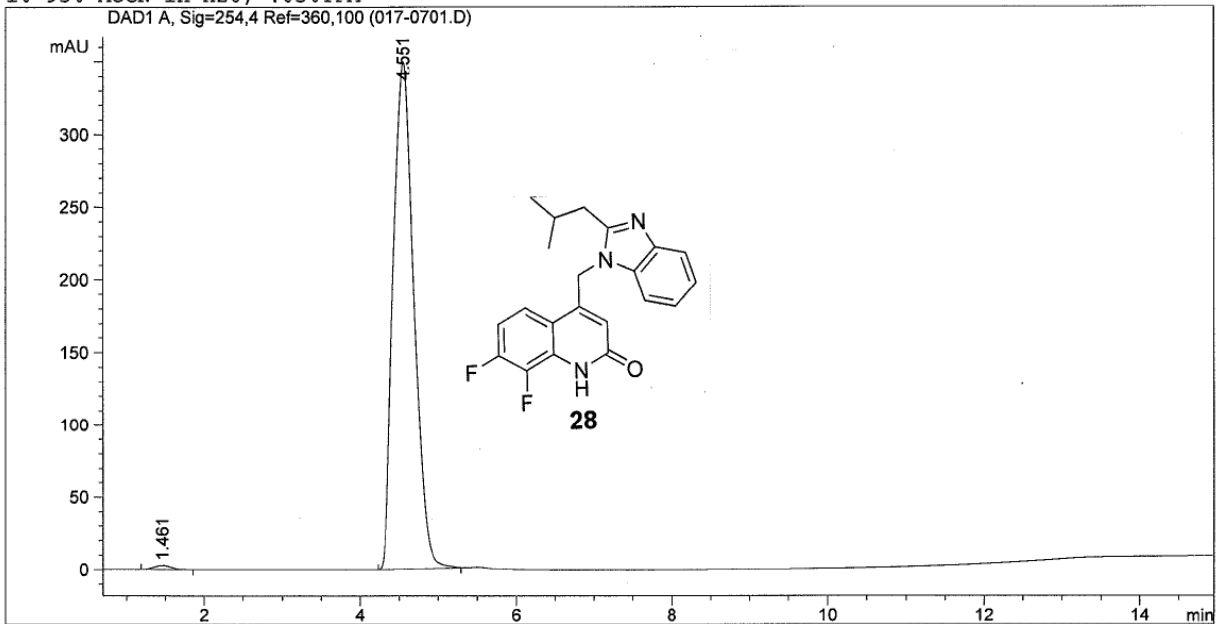




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=====
Injection Date   : 11/1/2007 4:37:25 PM           Seq. Line   :    7
Sample Name     :                               Location    : Vial 17
Acq. Operator   :                               Inj         :    1
Acq. Instrument : Kalypsys                       Inj Volume   : 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 11/1/2007 2:49:15 PM by 14
1%-95% AcCN in H2O, .05%TFA

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Area Percent Report
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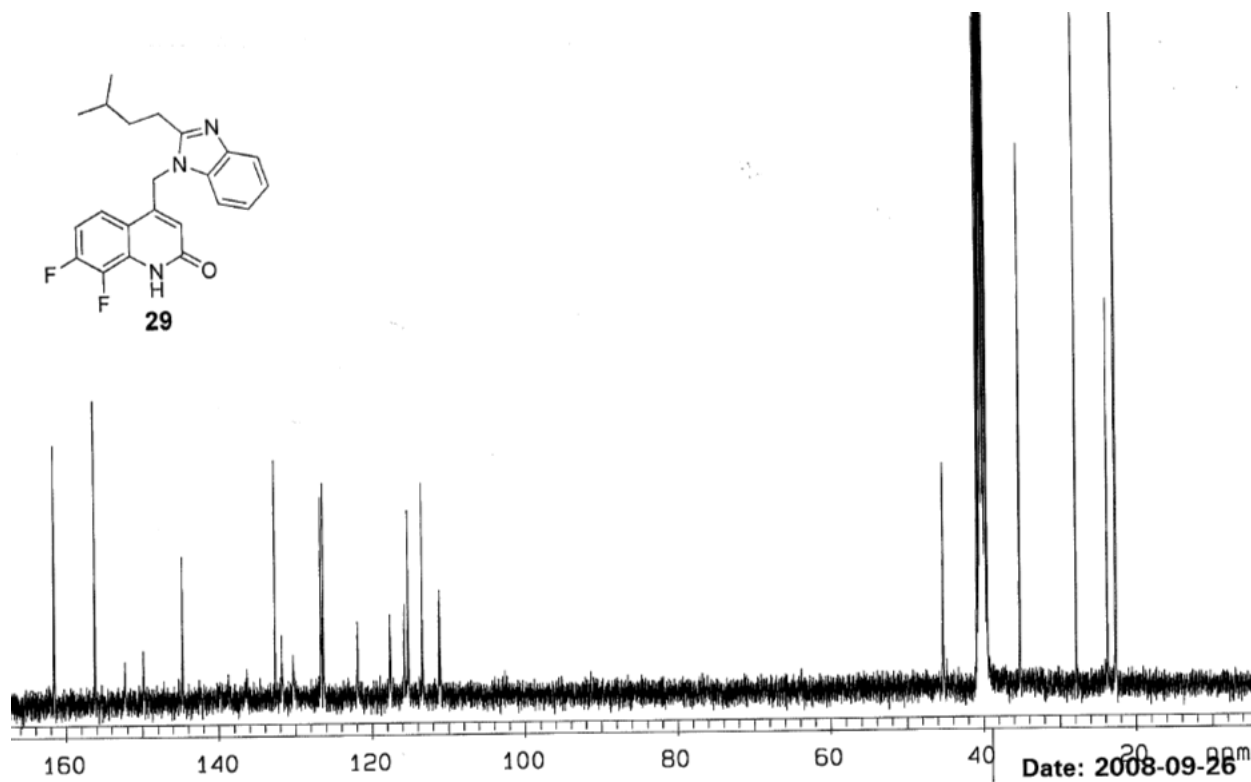
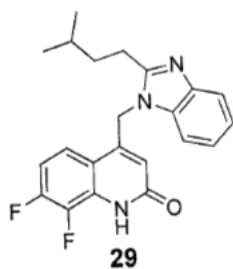
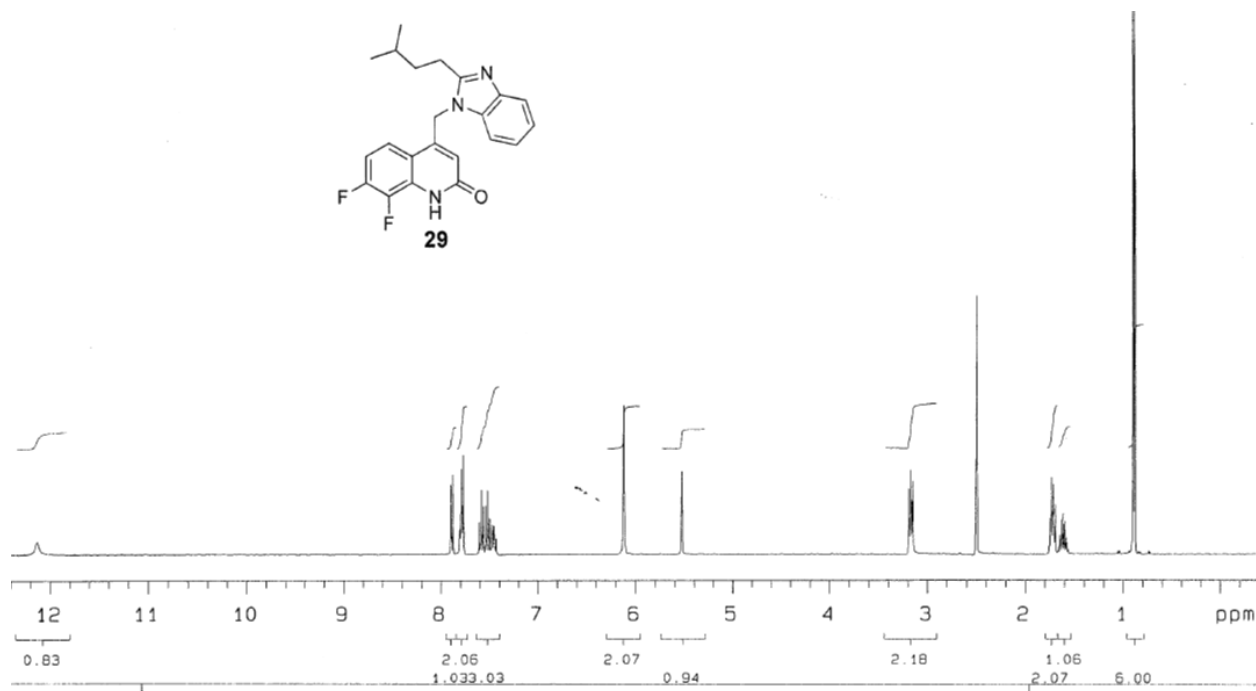
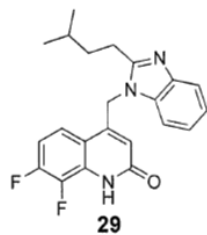
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

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Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.461	BB	0.2265	45.07879	2.94710	0.7042
2	4.551	BB	0.2923	6356.44385	349.34900	99.2958

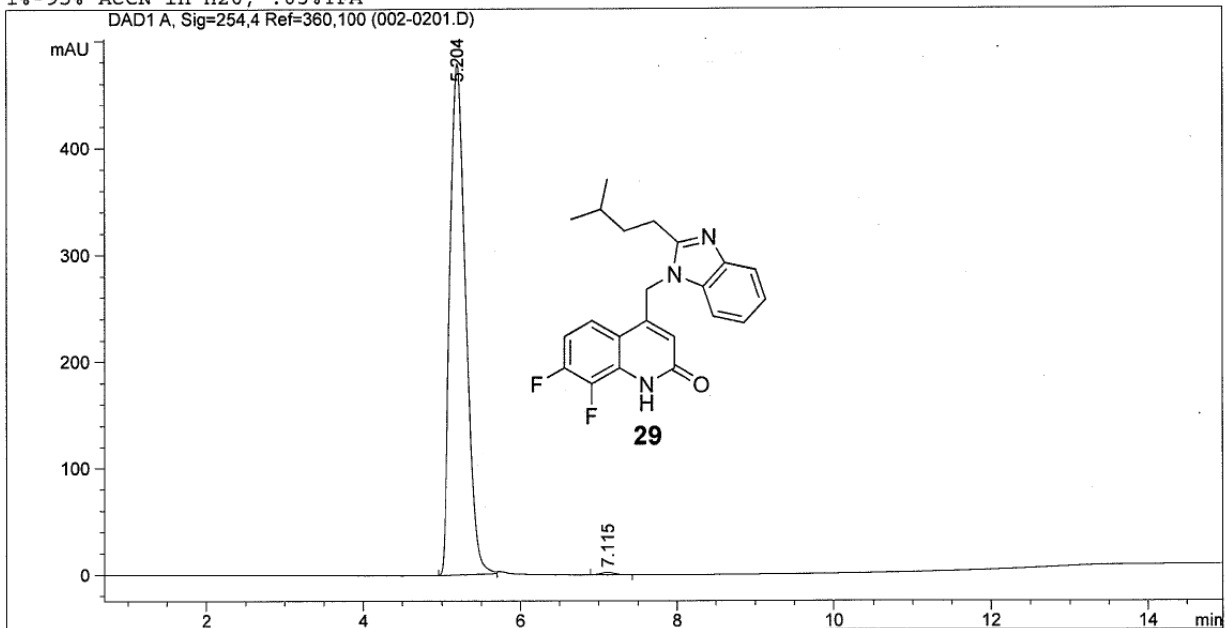
Compound 29: 7,8-Difluoro-4-((2-isopentyl-1H-benzo[d]imidazol-1-yl)methyl)quinolin-2(1H)-one



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=====
Injection Date   : 11/2/2007 9:12:26 AM           Seq. Line :    2
Sample Name     :                               Location  : Vial 2
Acq. Operator   :                               Inj       :    1
Acq. Instrument : Kalypsys                       Inj Volume: 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 11/2/2007 8:21:01 AM by 14
1%-95% AcCN in H2O, .05%TFA

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                          Area Percent Report
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Sorted By           :      Signal
Multiplier          :      1.0000
Dilution            :      1.0000
Use Multiplier & Dilution Factor with ISTDs

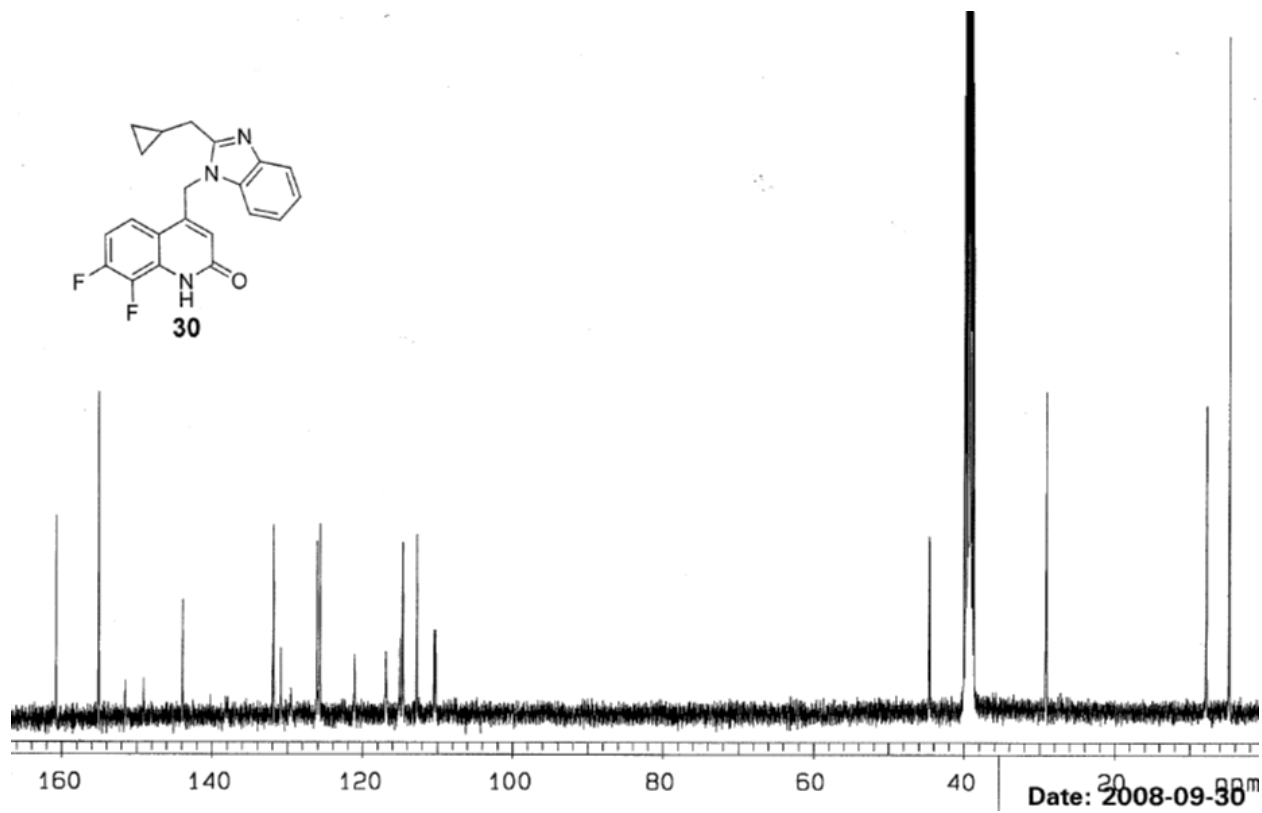
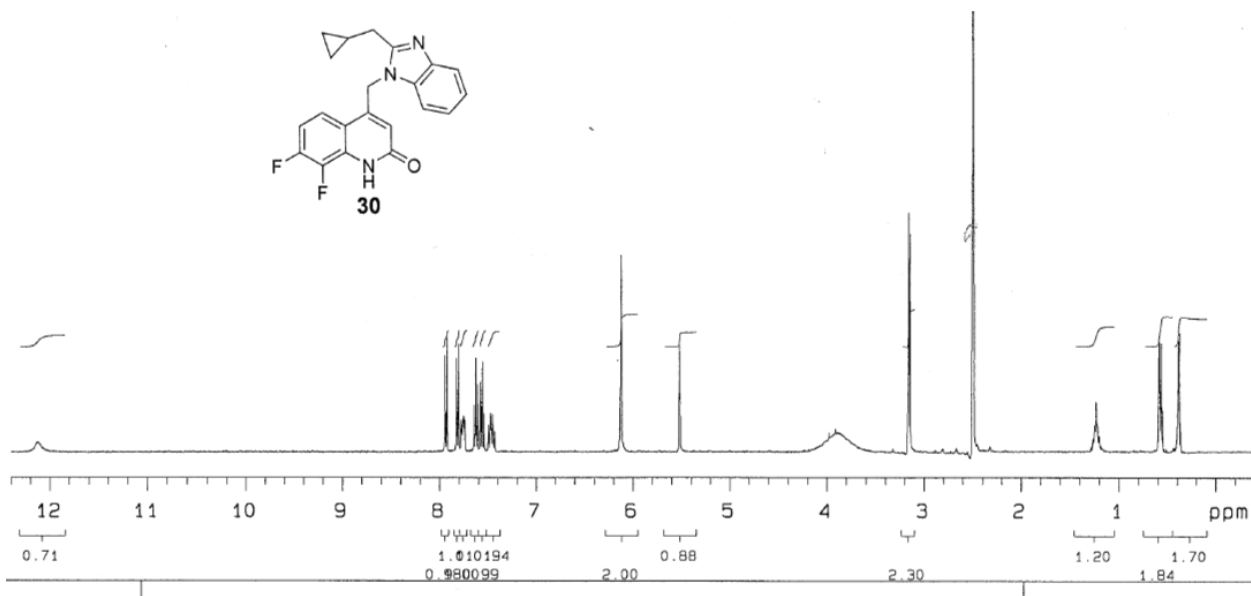
```

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.204	BB	0.2181	6649.56348	478.51587	99.5626
2	7.115	BB	0.1756	29.21431	2.37381	0.4374

Totals : 6678.77779 480.88968

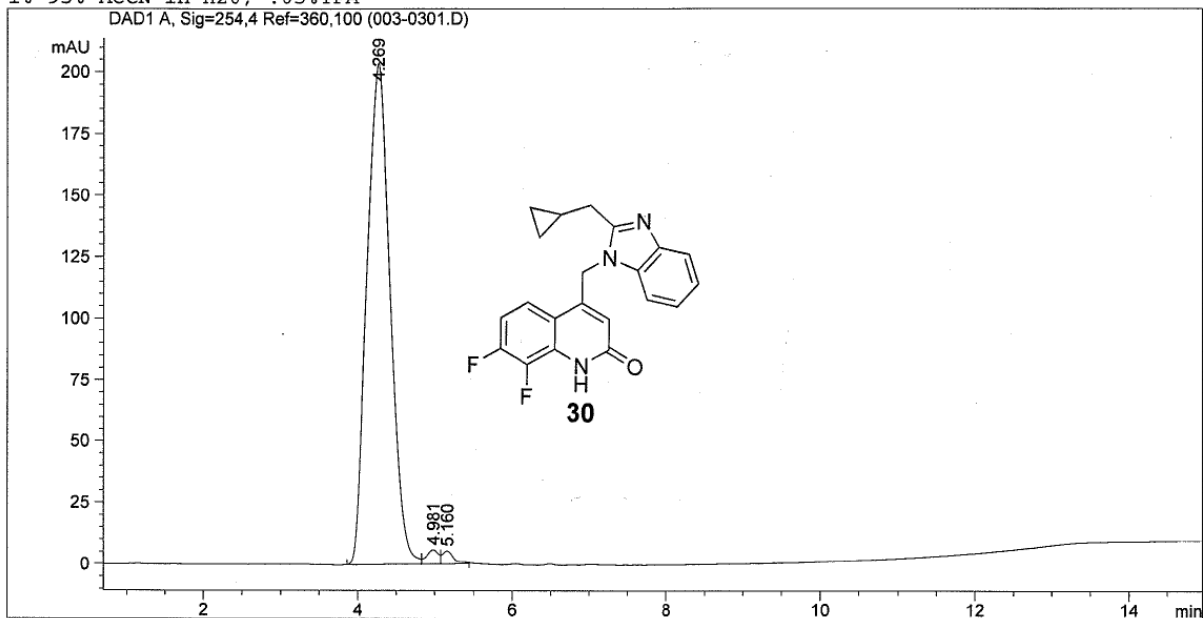
Compound 30: 4-((2-(Cyclopropylmethyl)-1H-benzimidazol-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



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=====
Injection Date : 11/2/2007 9:30:14 AM          Seq. Line : 3
Sample Name    :                               Location  : Vial 3
Acq. Operator  :                               Inj       : 1
Acq. Instrument: Kalypsys                      Inj Volume: 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/2/2007 8:21:01 AM by 14
1%-95% AcCN in H2O, .05%TFA

```



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Area Percent Report
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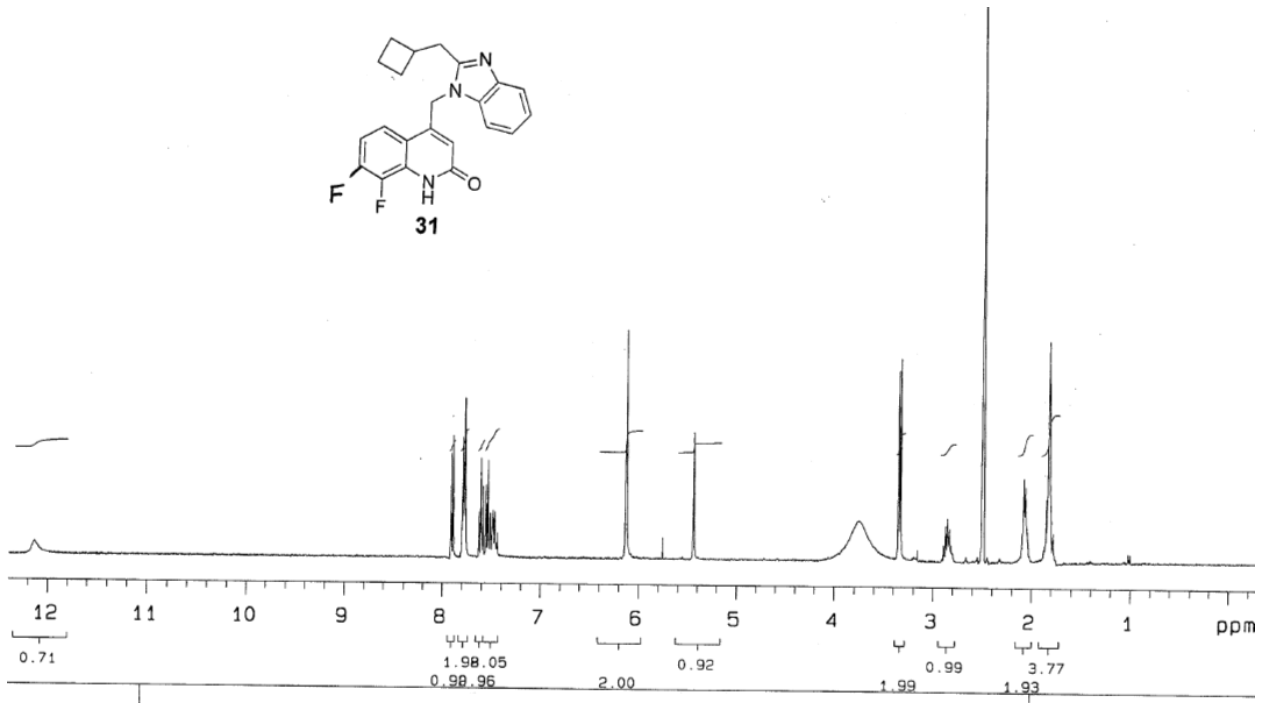
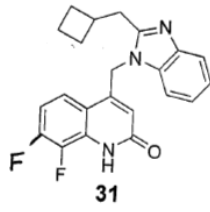
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

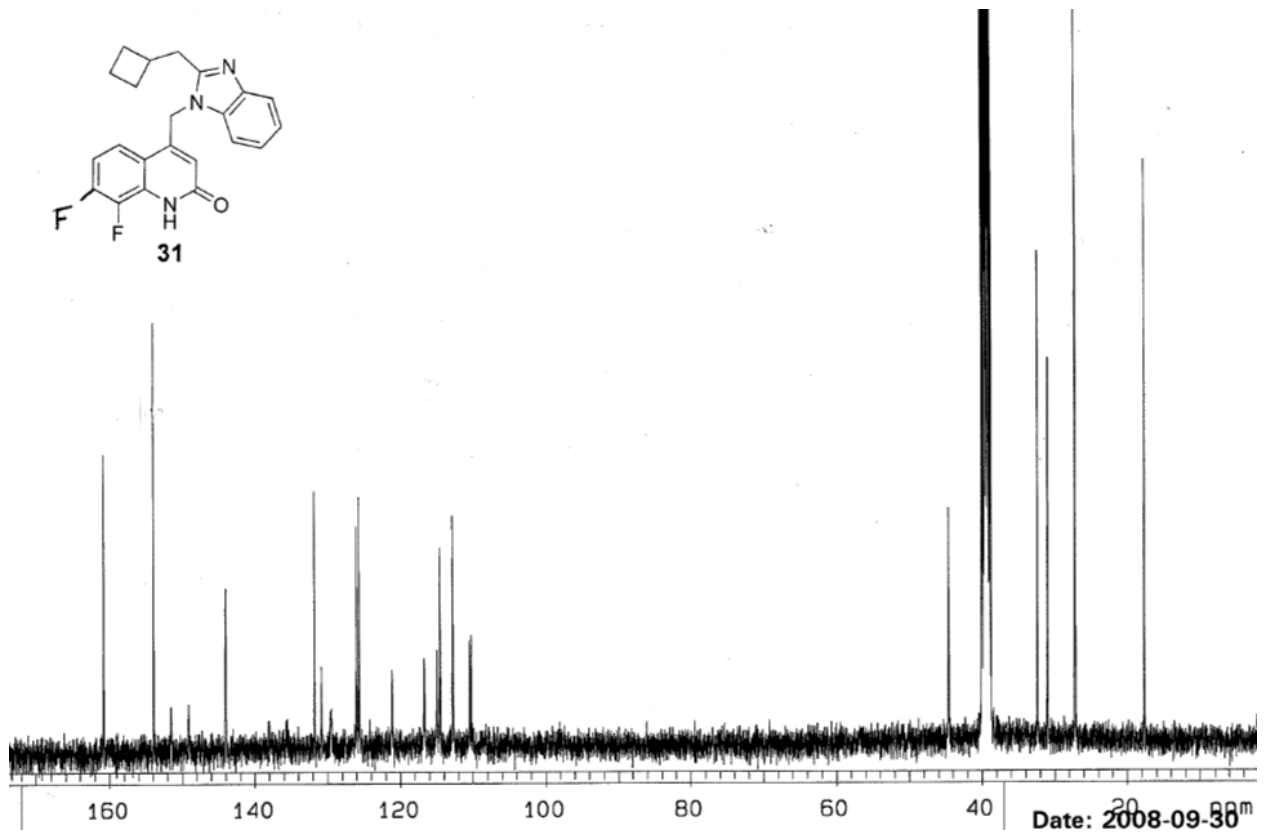
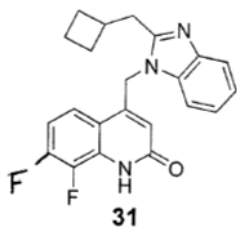
```

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.269	BV	0.3405	4272.53955	203.84377	97.4100
2	4.981	VV	0.1578	60.94324	5.74402	1.3894
3	5.160	VB	0.1532	52.65899	5.15437	1.2006

Compound 31: 4-((2-(Cyclobutylmethyl)-1H-benzo[d]imidazol-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-one

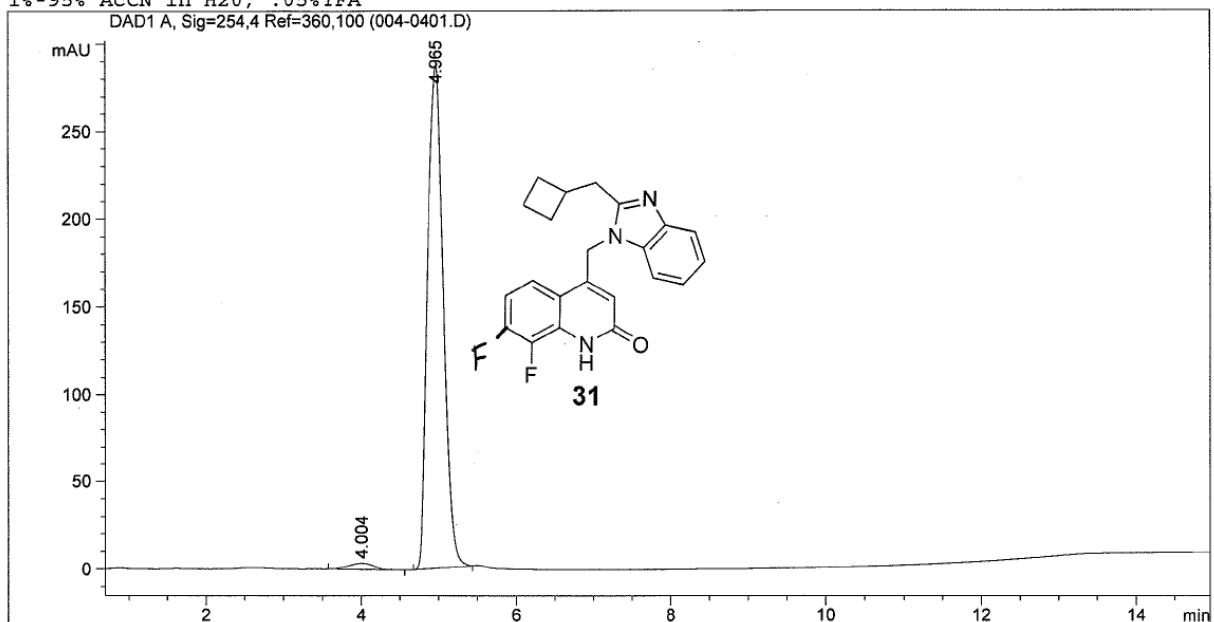




```

=====
Injection Date : 11/2/2007 9:47:58 AM      Seq. Line : 4
Sample Name    :                            Location  : Vial 4
Acq. Operator  : 14                        Inj       : 1
Acq. Instrument : Kalypsys                  Inj Volume: 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/2/2007 8:21:01 AM by 14
1%-95% AcCN in H2O, .05%TFA

```



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Area Percent Report
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```

Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

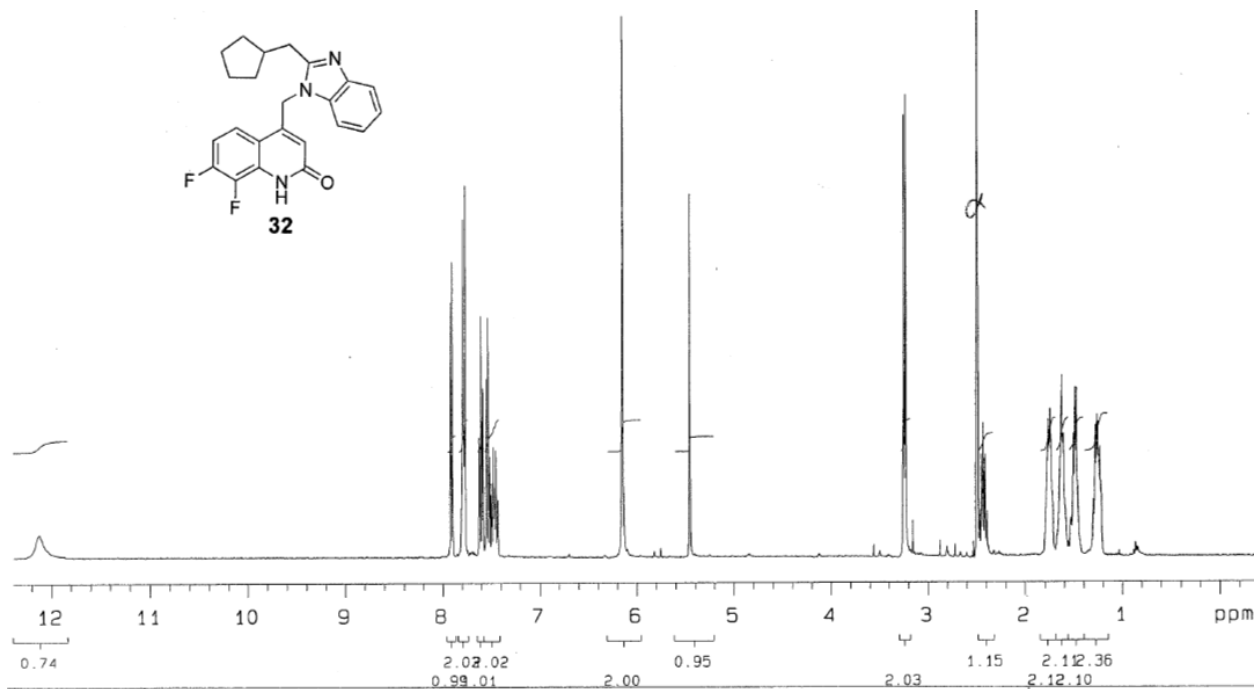
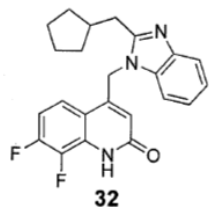
```

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.004	BB	0.3038	78.74367	3.53615	1.9038
2	4.965	BB	0.2268	4057.43286	287.29013	98.0962

Totals : 4136.17653 290.82628

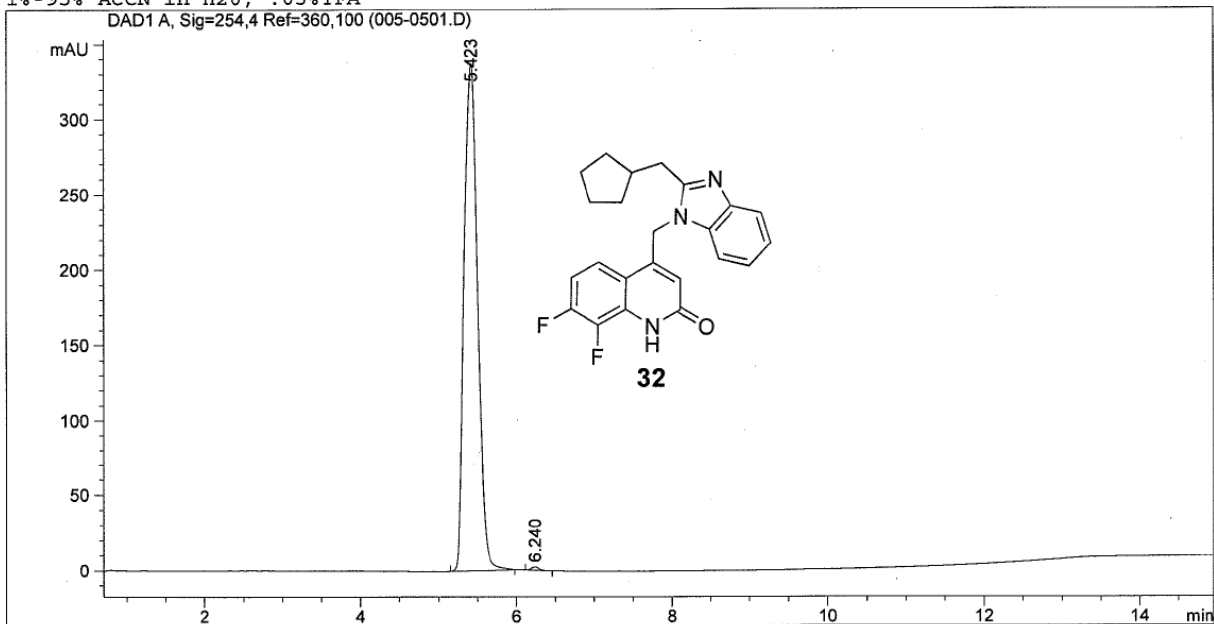
Compound 32: 4-((2-(Cyclopentylmethyl)-1H-benzo[d]imidazol-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



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=====
Injection Date   : 11/2/2007 10:05:44 AM           Seq. Line :    5
Sample Name     :                               Location  : Vial 5
Acq. Operator   : 14                             Inj       :    1
Acq. Instrument : Kalypsys                         Inj Volume: 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 11/2/2007 8:21:01 AM by 14
1%-95% AcCN in H2O, .05%TFA

```



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Area Percent Report
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Sorted By       :      Signal
Multiplier      :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

```

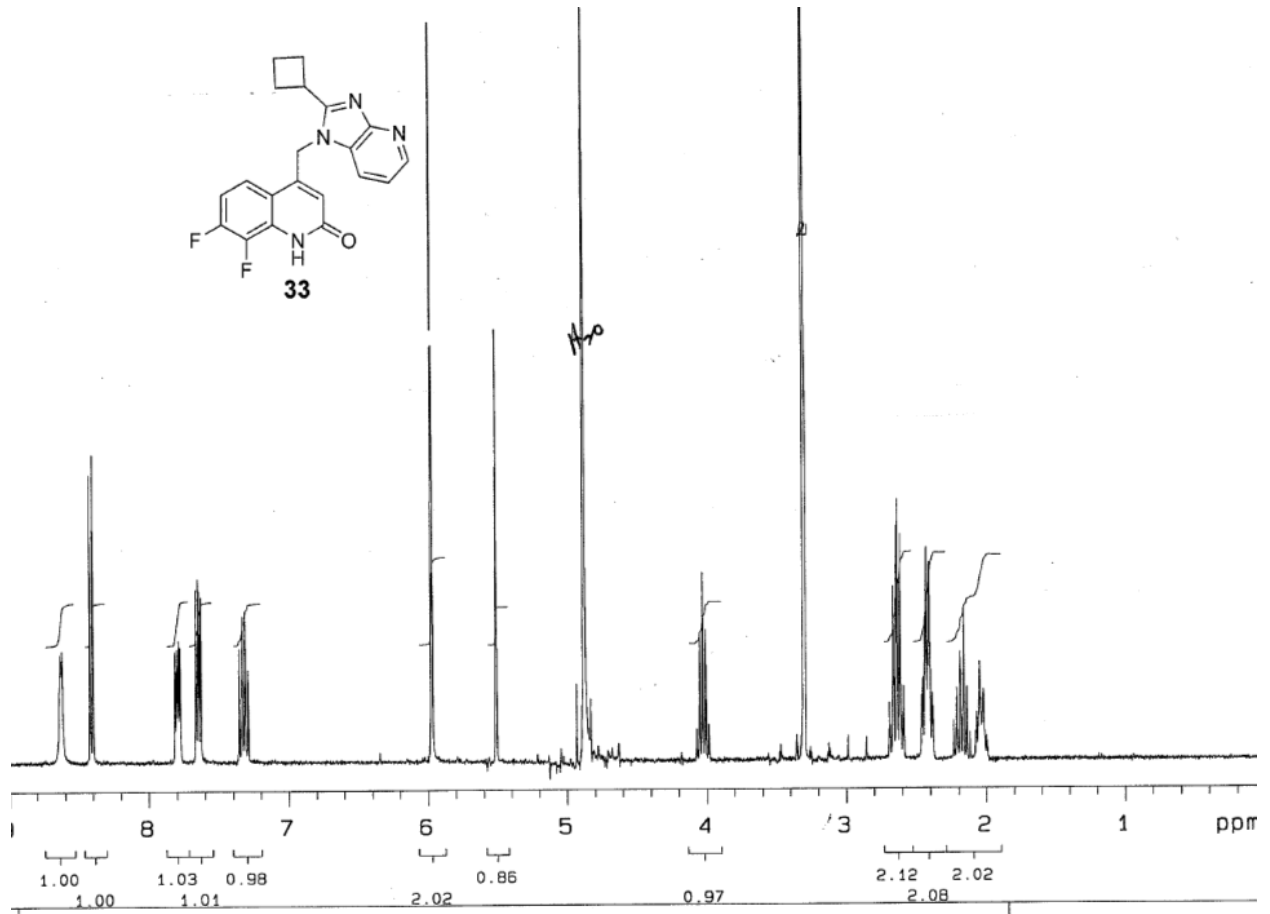
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.423	BB	0.1906	4002.94824	336.96768	99.6345
2	6.240	BB	0.1114	14.68244	2.15841	0.3655

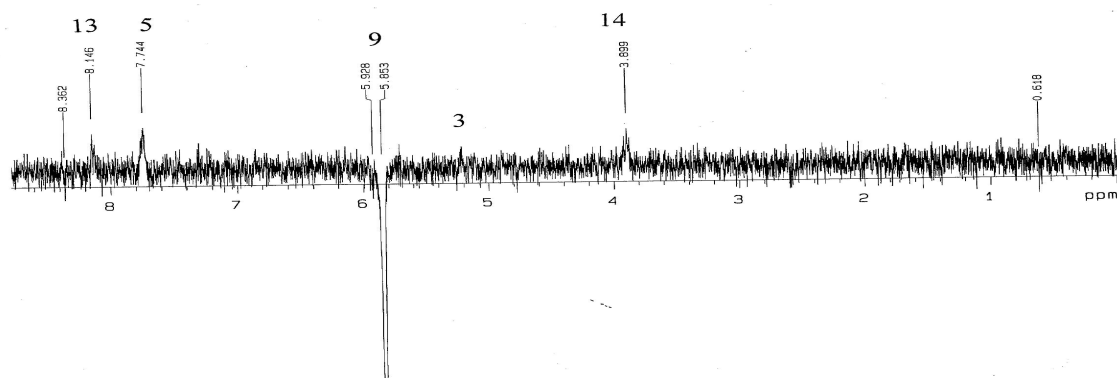
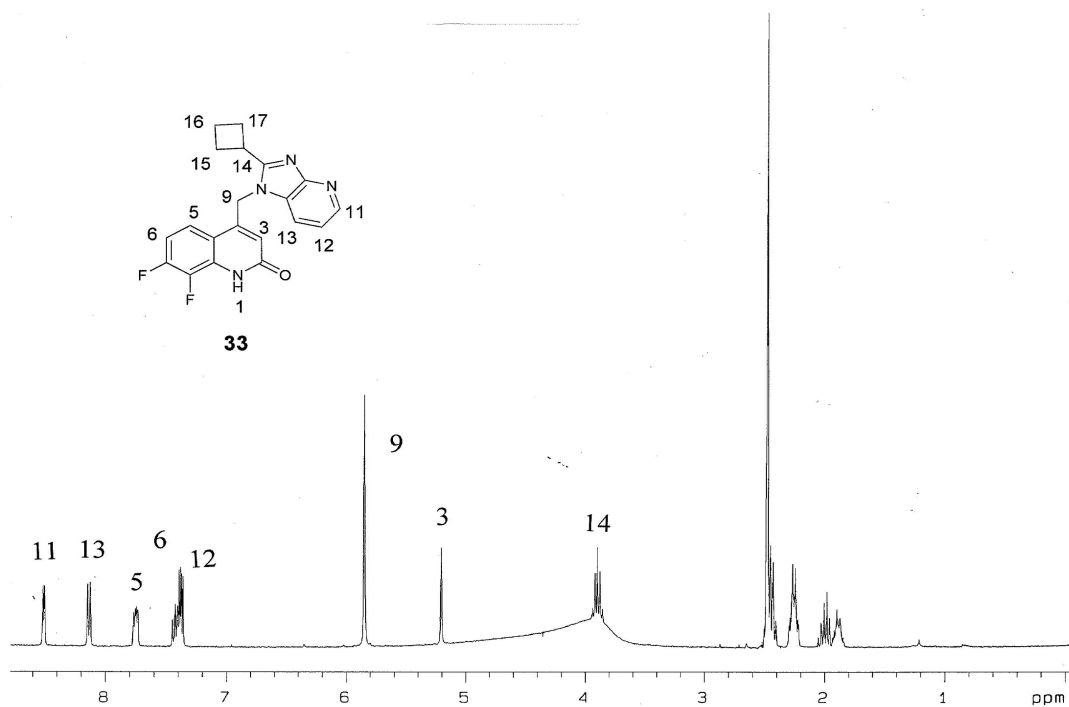
Totals : 4017.63068 339.12609

Compound 33: 4-((2-Cyclobutyl-1H-imidazo[4,5-b]pyridin-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-

one



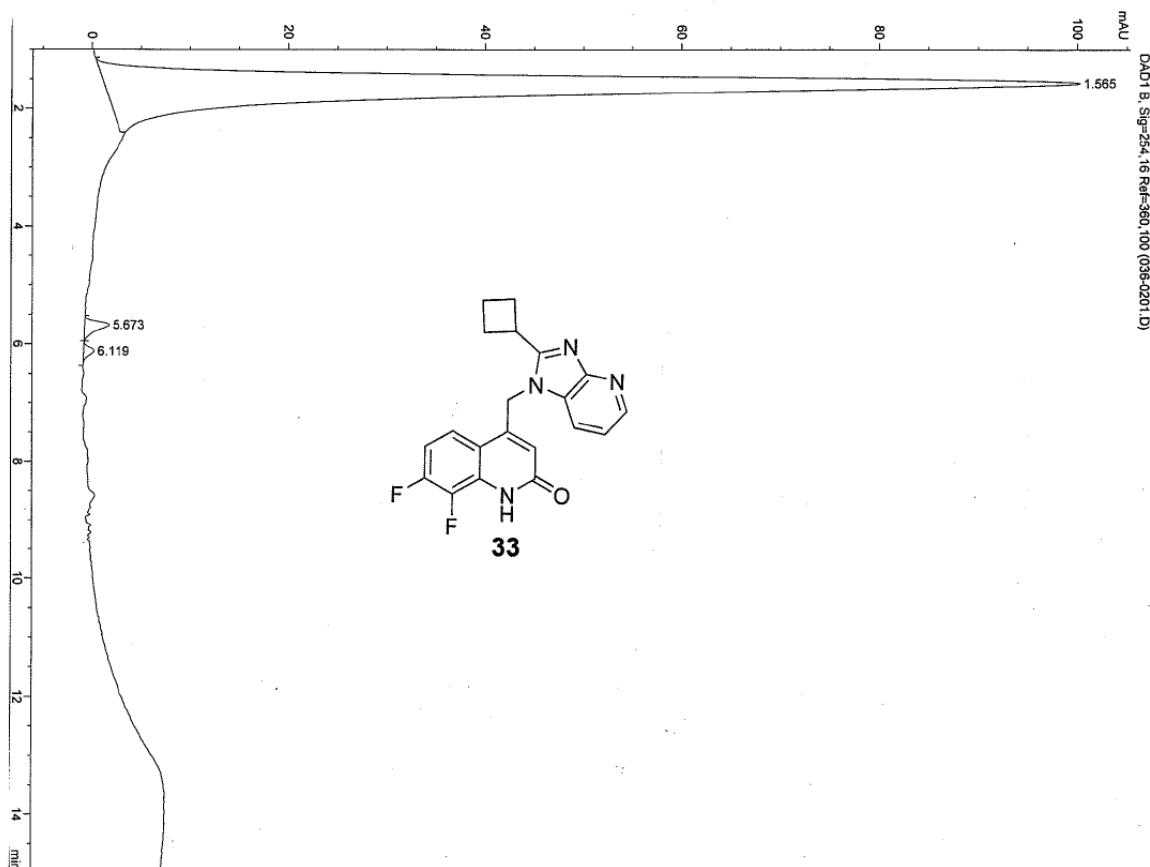
NOE for Compound 33



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=====
Injection Date : 11/3/2008 10:38:27 AM      Seq. Line : 2
Sample Name    :                               Location : Vial 36
Acq. Operator  :                               Inj : 1
Acq. Instrument : Kalypsys                     Inj Volume : 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/3/2008 10:20:09 AM by 1
1%-95% AcCN in H2O, .05%TFA
=====

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Area Percent Report

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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

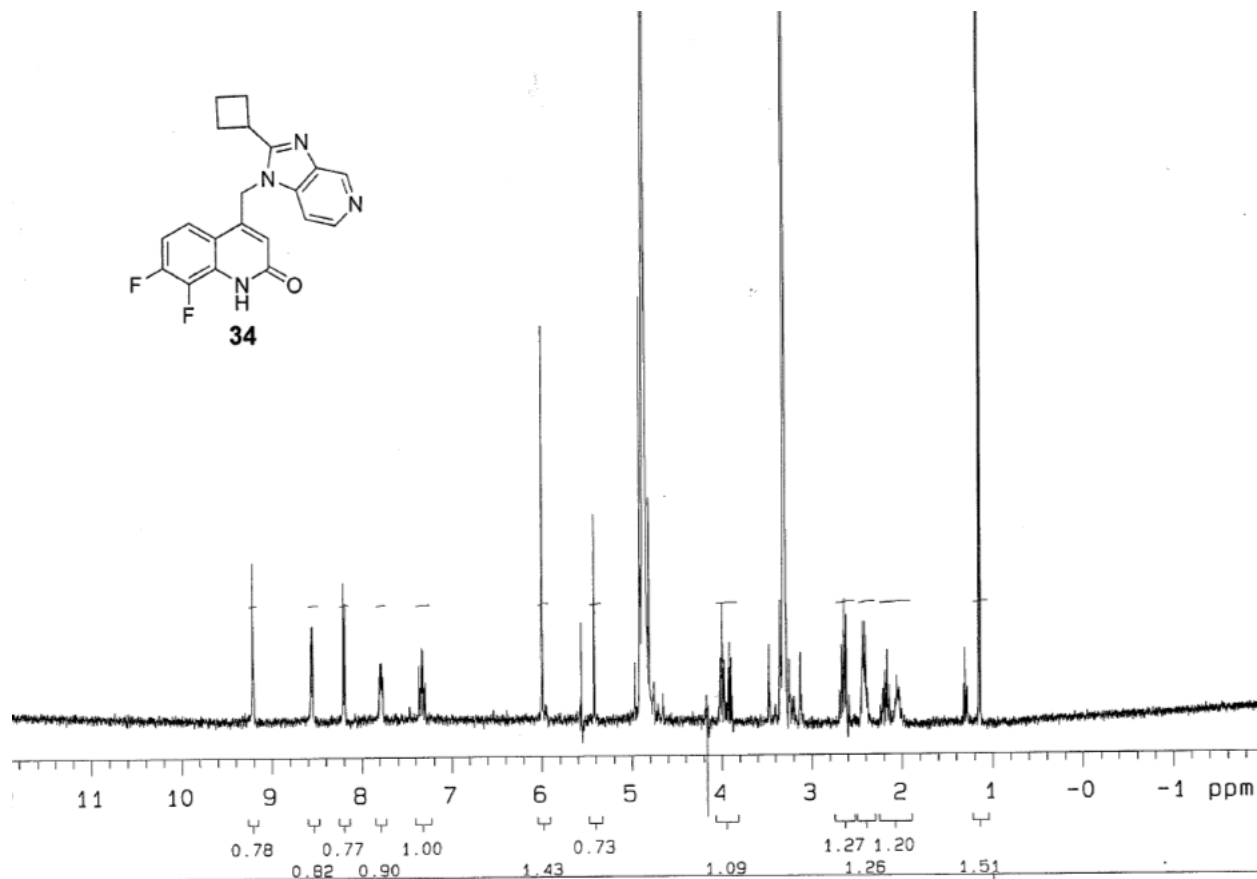
```

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

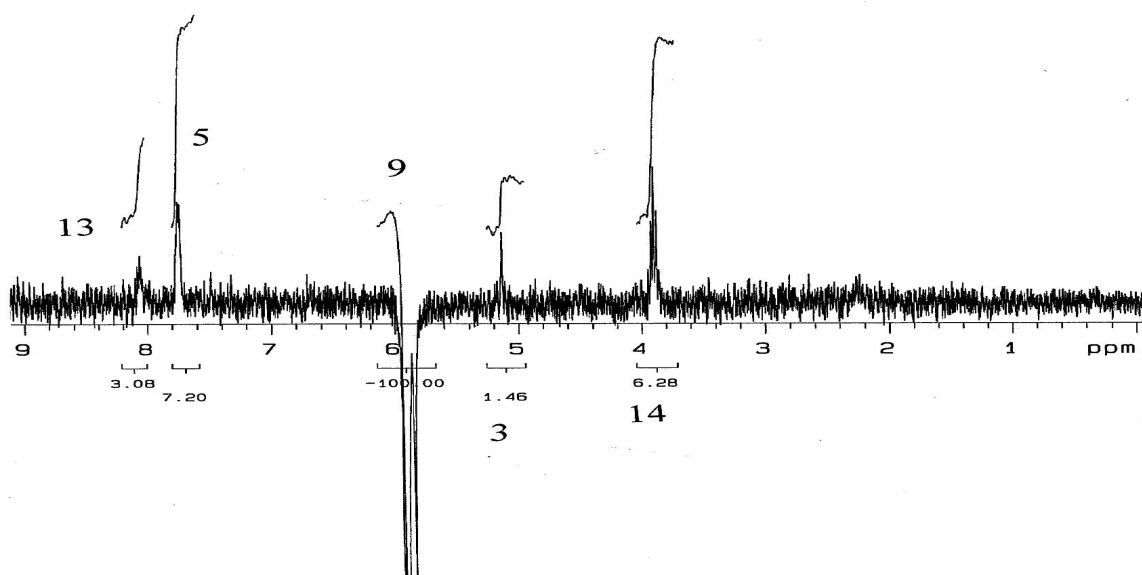
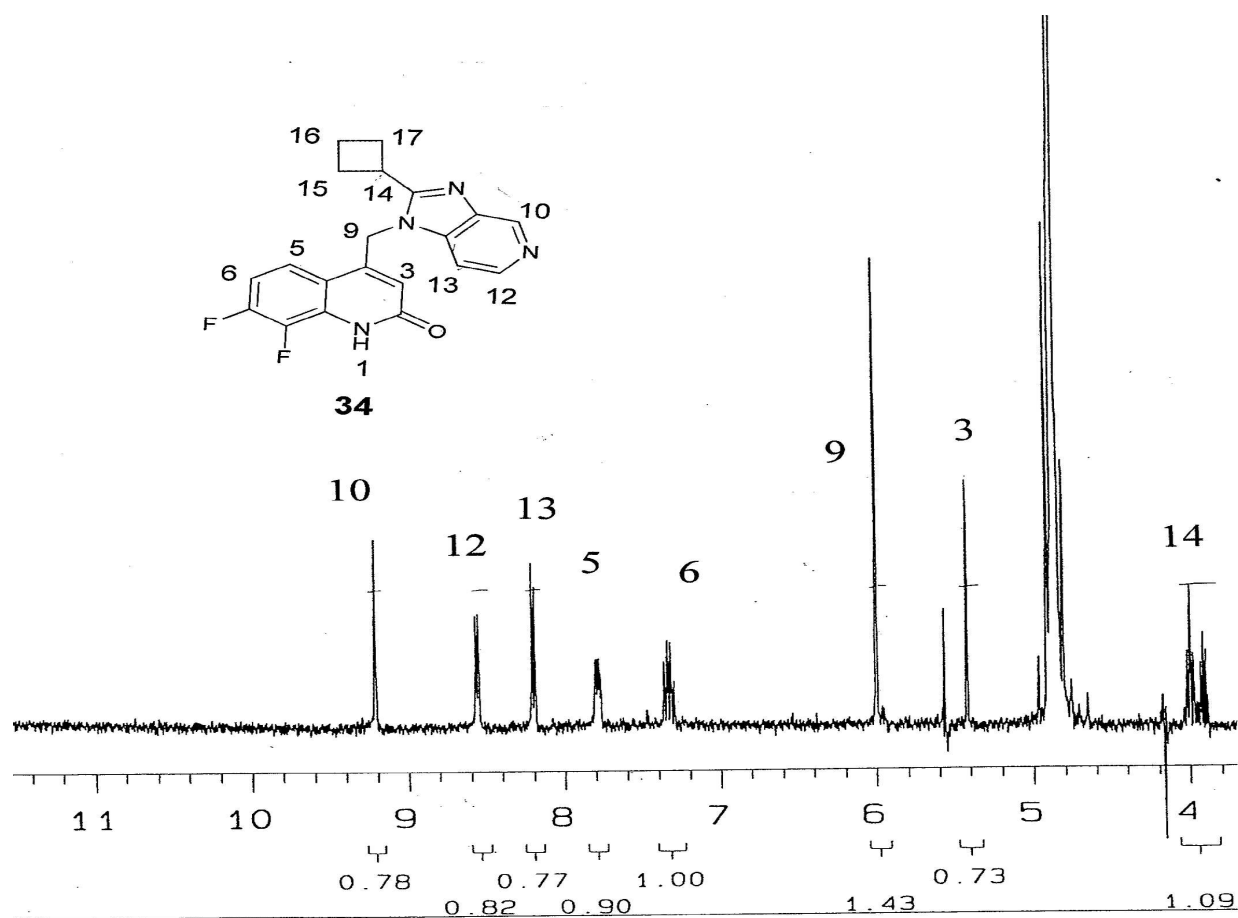
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.565	BB	0.3250	2165.80811	99.10806	98.3515
2	5.673	BB	0.1583	26.13092	2.49195	1.1866
3	6.119	BB	0.1493	10.17012	1.04685	0.4618

Totals : 2202.10915 102.64686

Compound 34: 4-((2-Cyclobutyl-1H-imidazo[4,5-c]pyridin-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



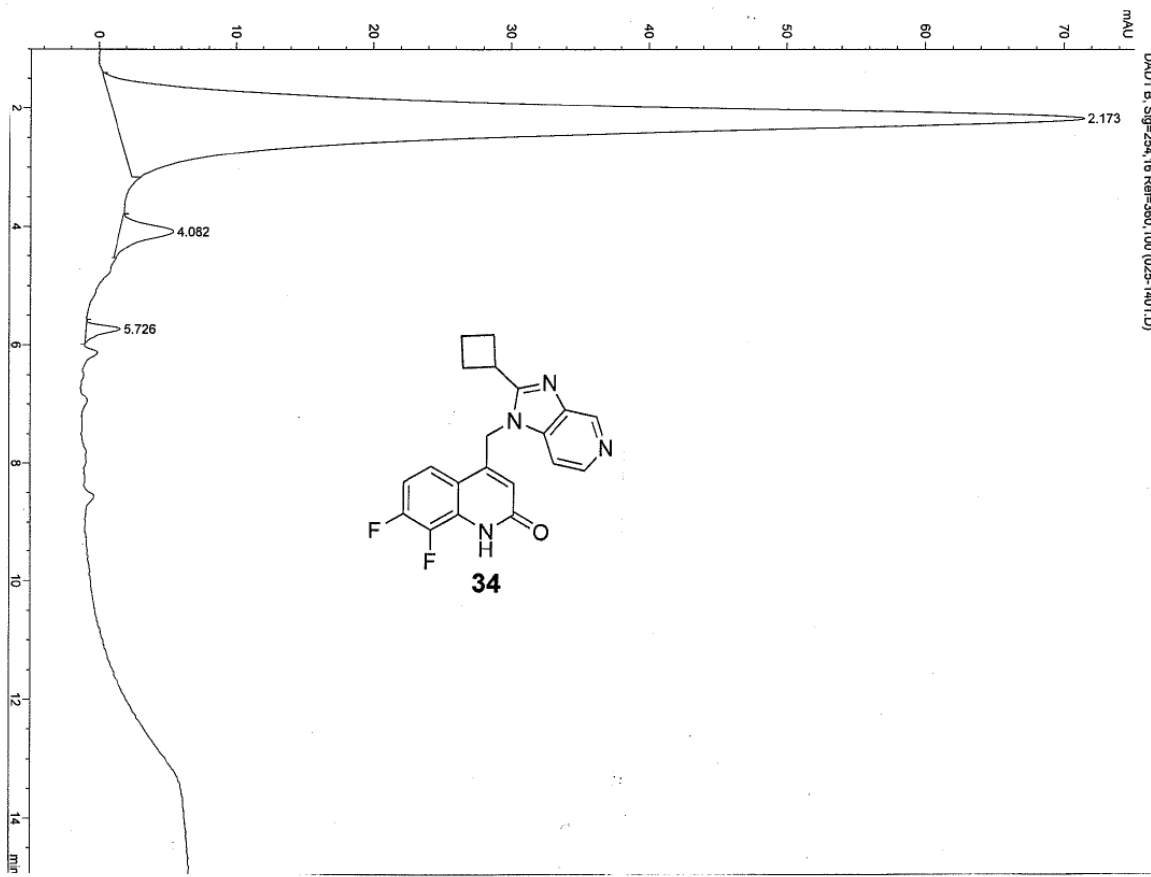
NOE for Compound 34



```

=====
Injection Date : 10/31/2008 12:16:01 PM      Seq. Line : 14
Sample Name    :                               Location  : Vial 25
Acq. Operator  : 1                             Inj       : 1
Acq. Instrument : Kalypsys                      Inj Volume: 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 10/31/2008 8:33:04 AM by 1
1%-95% AcCN in H2O, .05%TFA
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Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution      :      1.0000
Use Multiplier & Dilution Factor with ISTDs

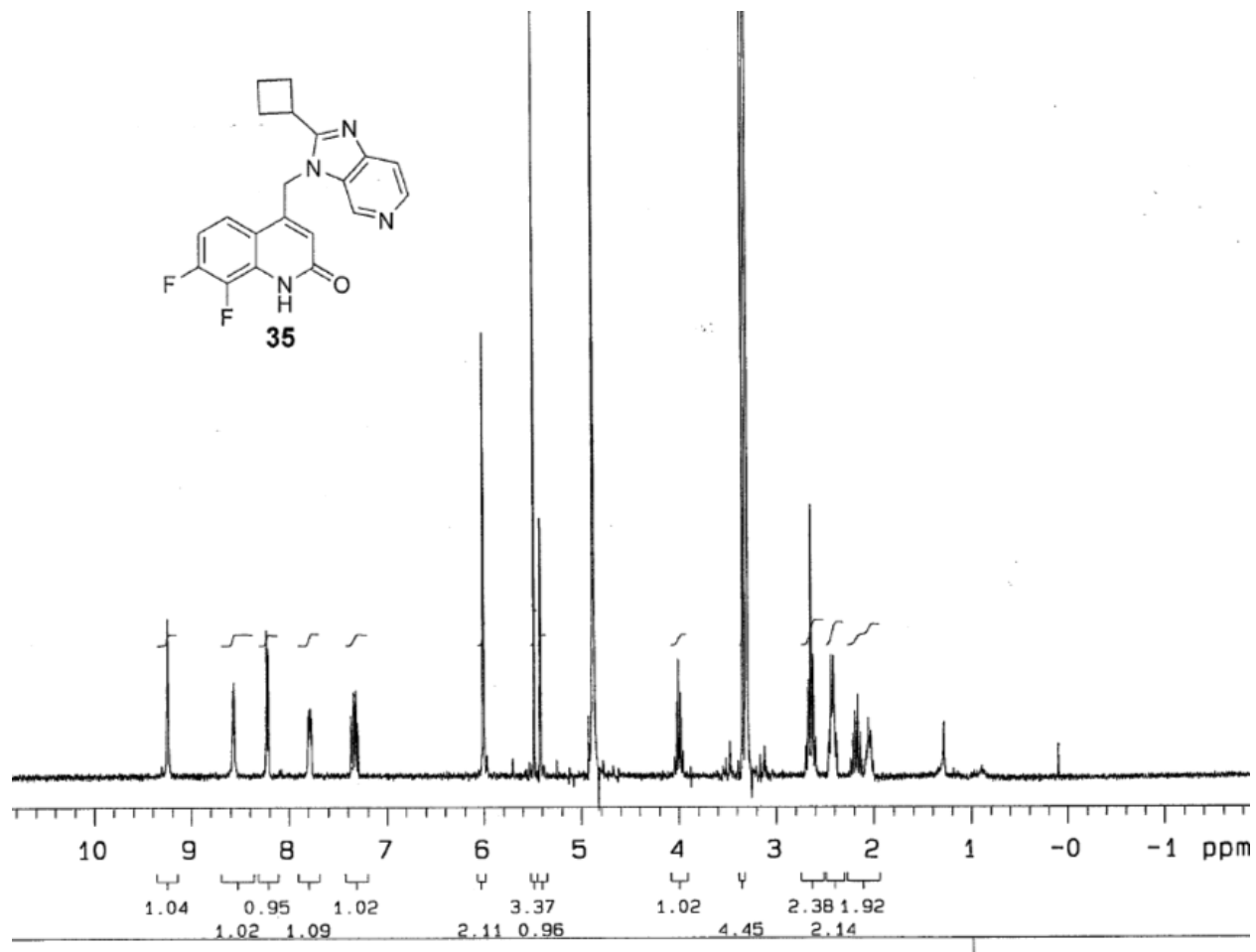
```

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.173	BB	0.4860	2397.87939	70.28938	96.1800
2	4.082	BB	0.2645	72.02435	3.95485	2.8889
3	5.726	BB	0.1427	23.21169	2.49058	0.9310

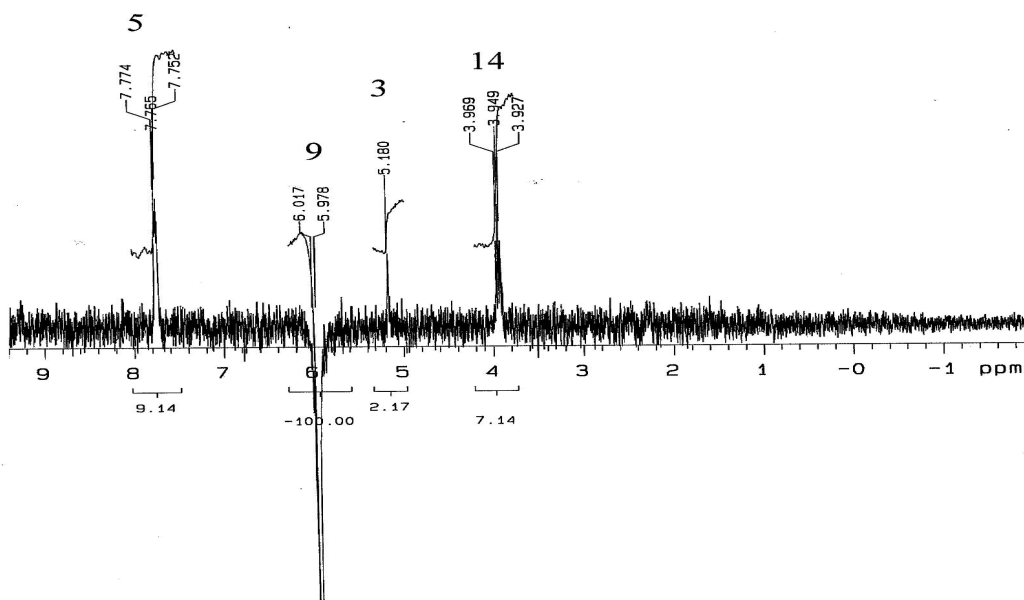
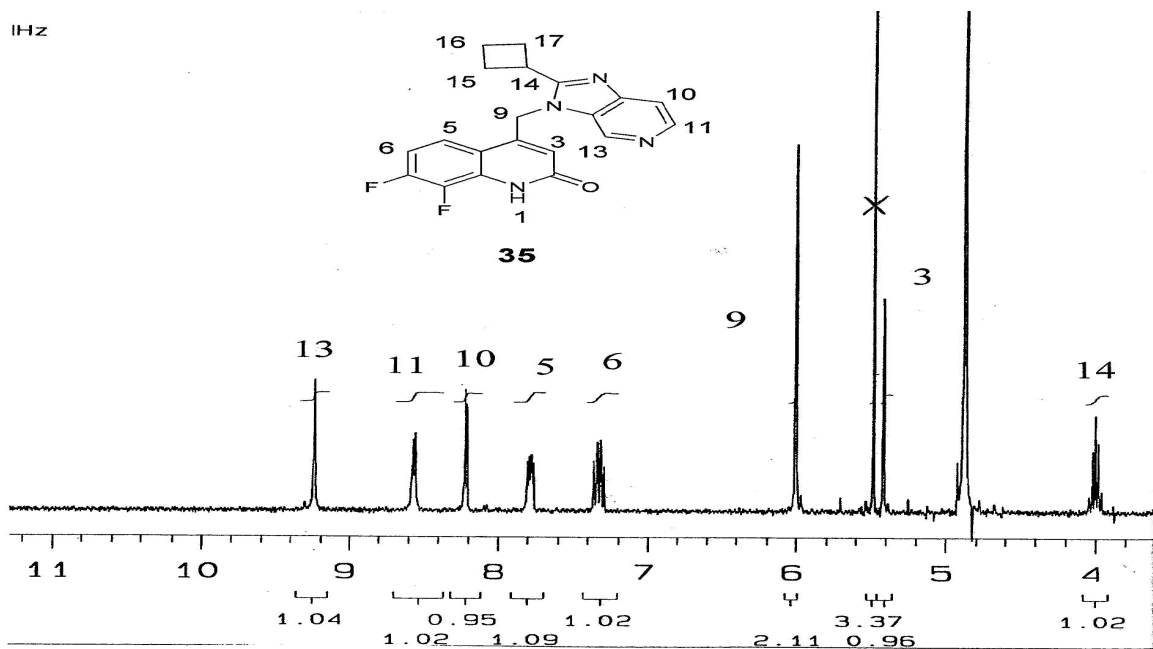
Totals : 2493.11544 76.73481

Compound 35: 4-((2-Cyclobutyl-3H-imidazo[4,5-c]pyridin-3-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



NOE for Compound 35

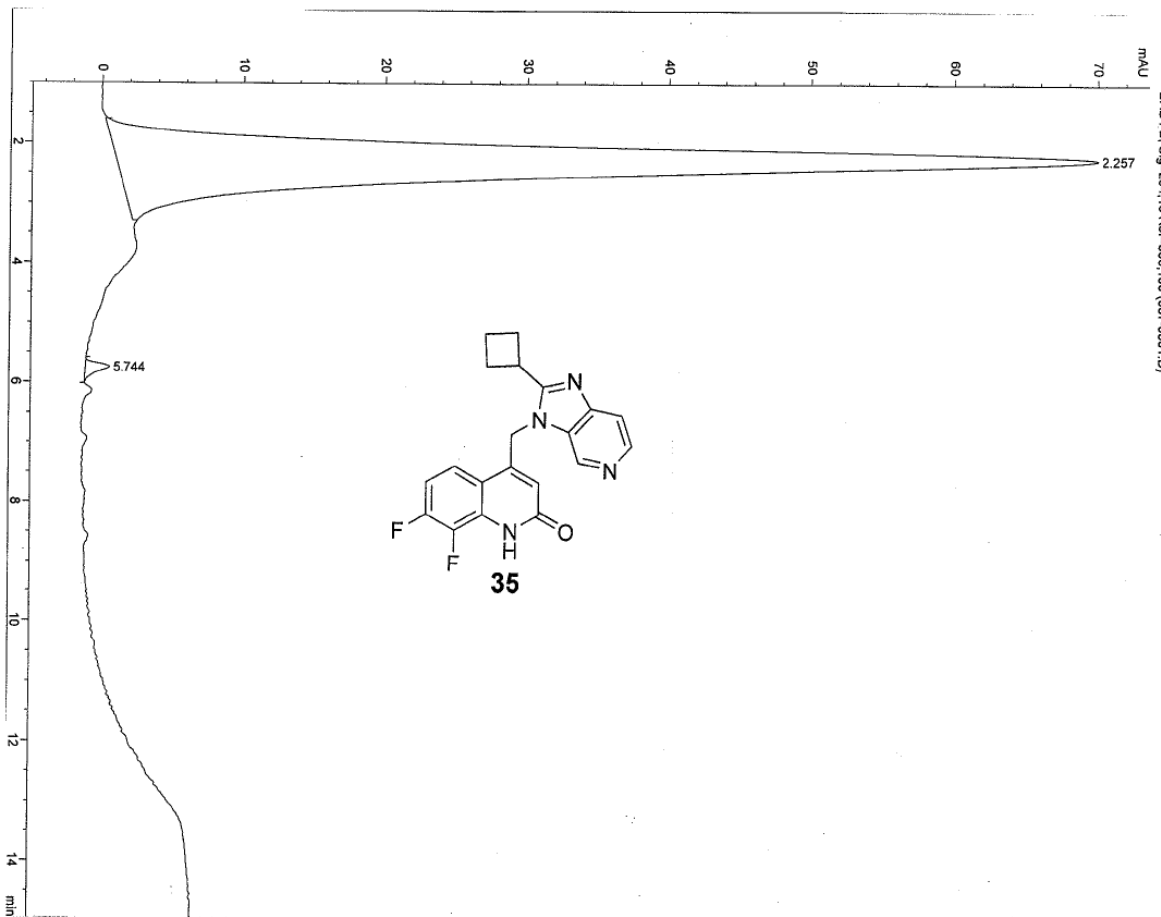
1H NMR



```

=====
Injection Date : 11/3/2008 10:55:33 AM      Seq. Line : 3
Sample Name    :                               Location  : Vial 37
Acq. Operator  :                               Inj       : 1
Acq. Instrument : Kalypsys                     Inj Volume: 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/3/2008 10:20:09 AM by 1
1%-95% AcCN in H2O, .05%TFA
=====

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Area Percent Report

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Sorted By      : Signal
Multiplier     : 1.0000
Dilution      : 1.0000
Use Multiplier & Dilution Factor with ISTDs

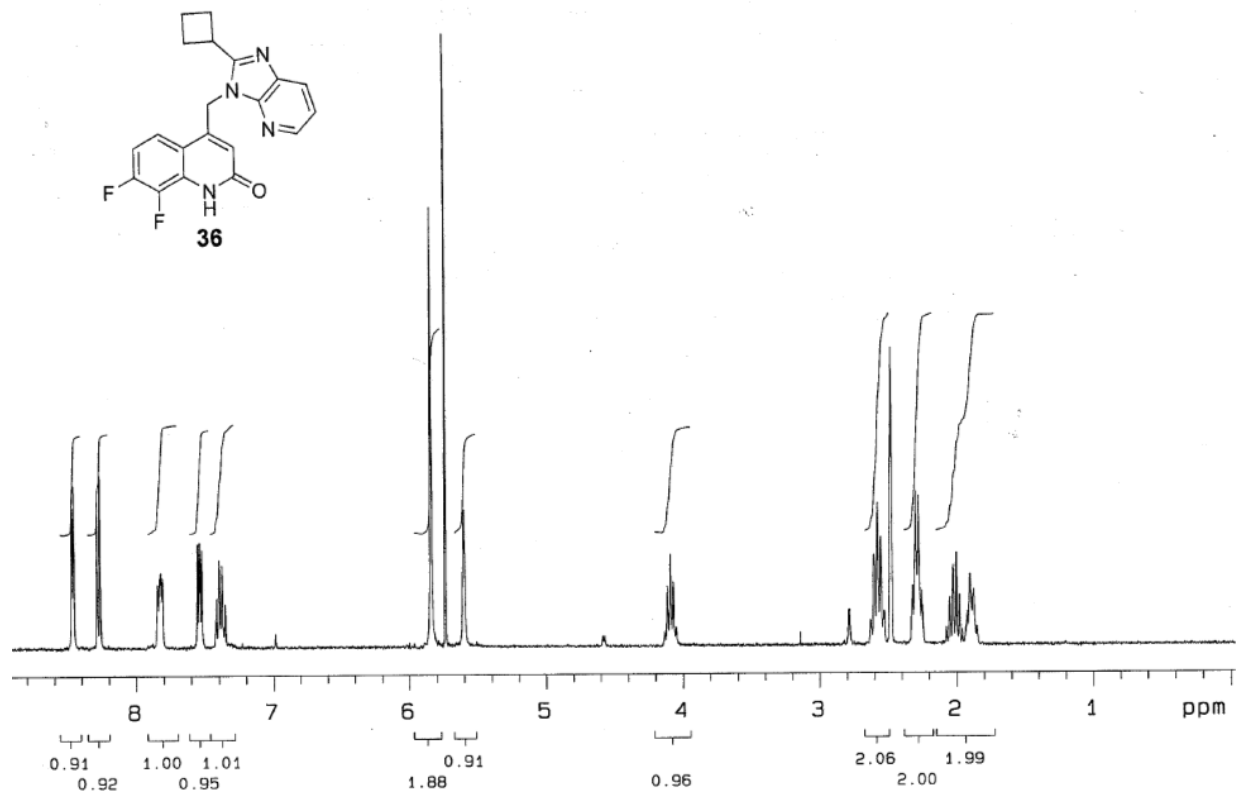
```

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

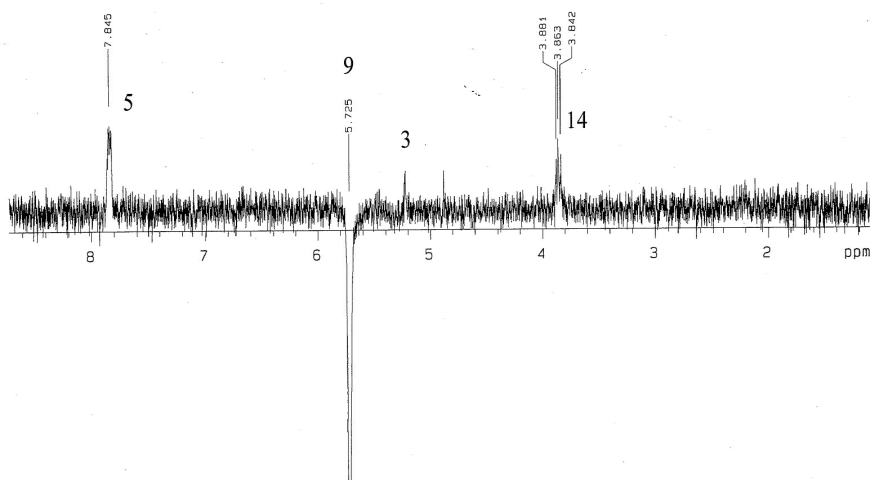
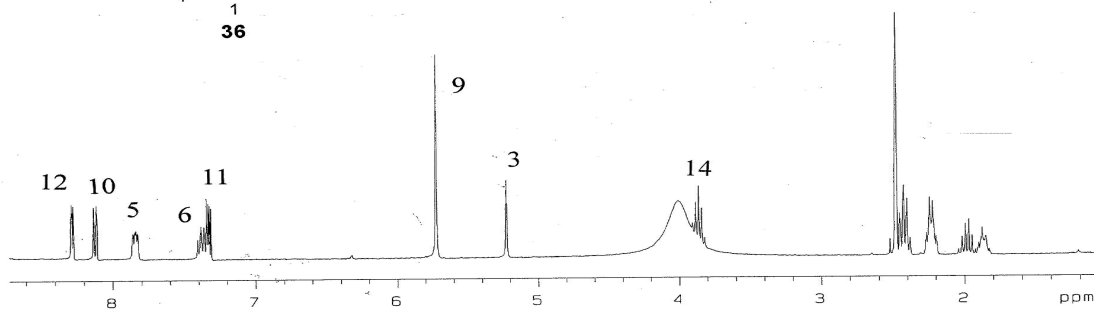
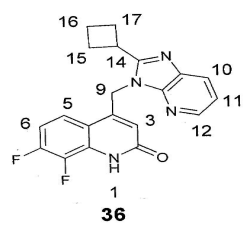
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.257	BB	0.4809	2278.68799	69.07603	99.2905
2	5.744	BB	0.1473	16.28327	1.67669	0.7095

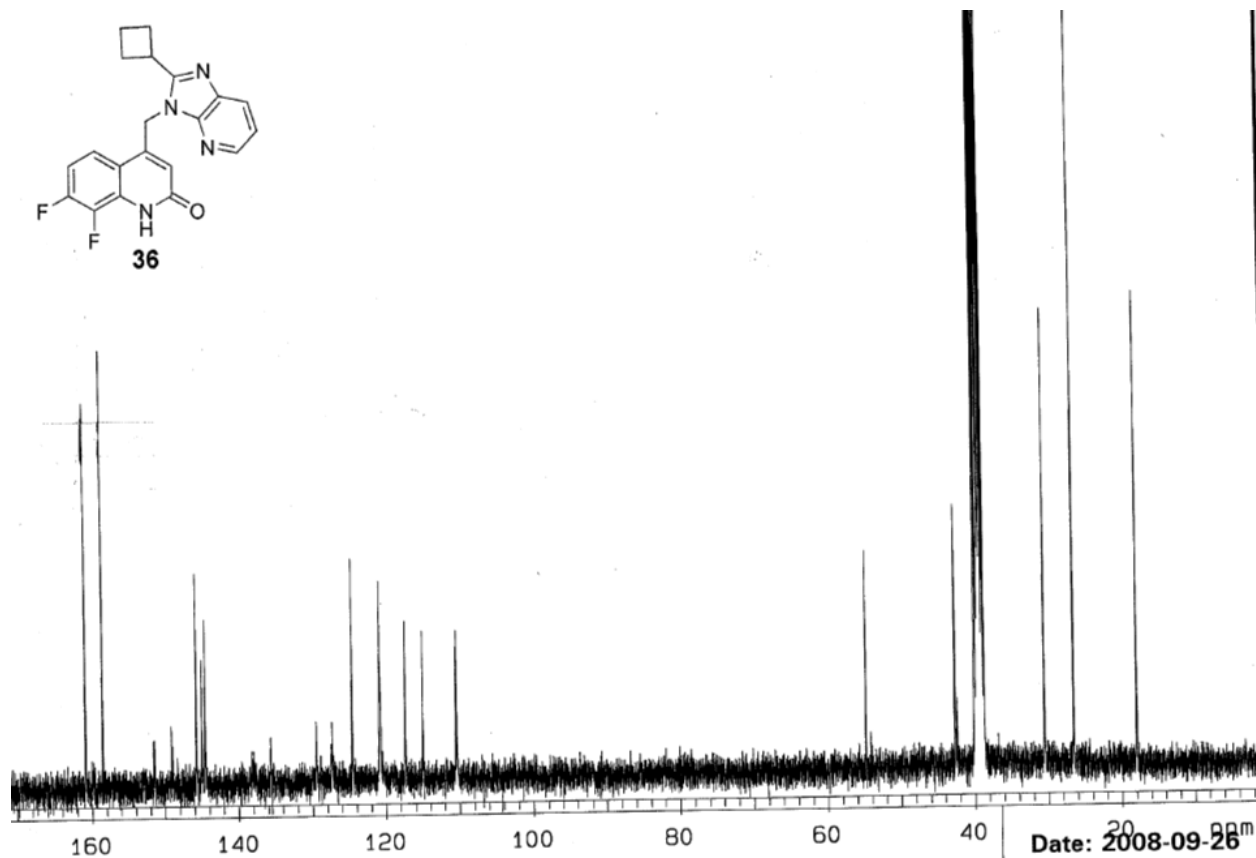
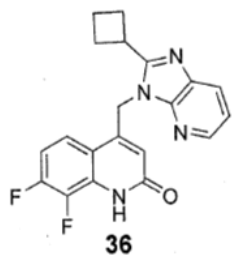
Totals : 2294.97126 70.75272

Compound 36: 4-((2-Cyclobutyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



NOE for Compound 36

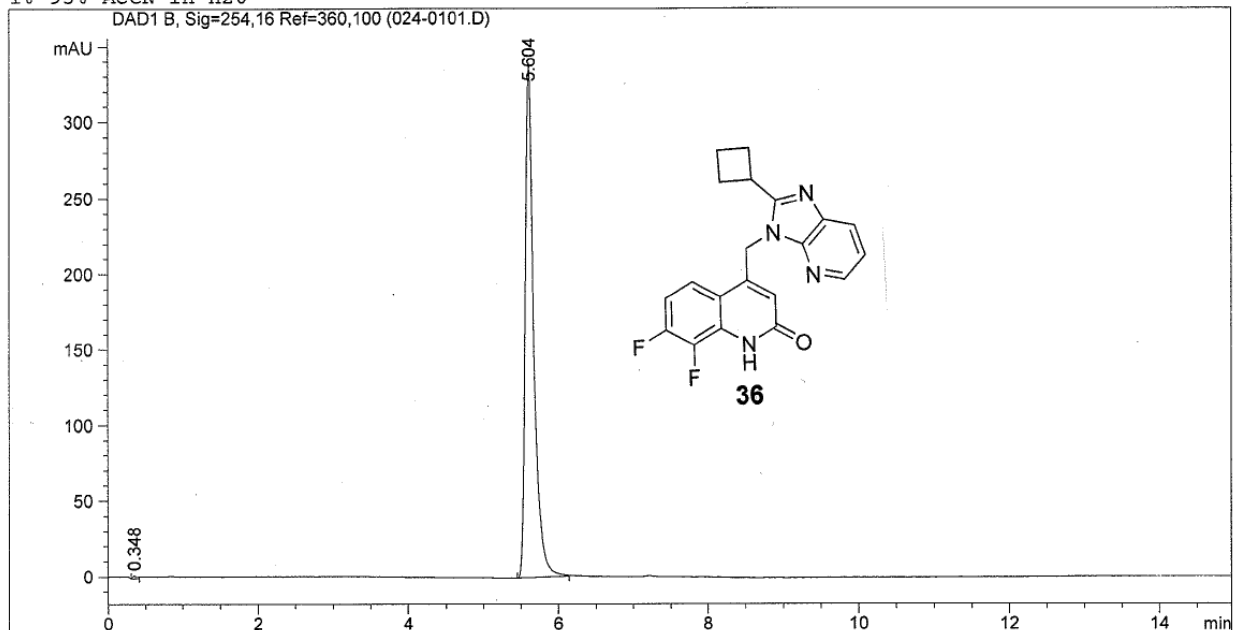




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=====
Injection Date   : 3/25/2009 6:20:16 PM           Seq. Line :    1
Sample Name     :                               Location  : Vial 24
Acq. Operator   : 1                               Inj       :    1
Acq. Instrument : Kalypsys                        Inj Volume: 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 3/25/2009 6:19:22 PM by 1
1%-95% AcCN in H2O

```



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Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

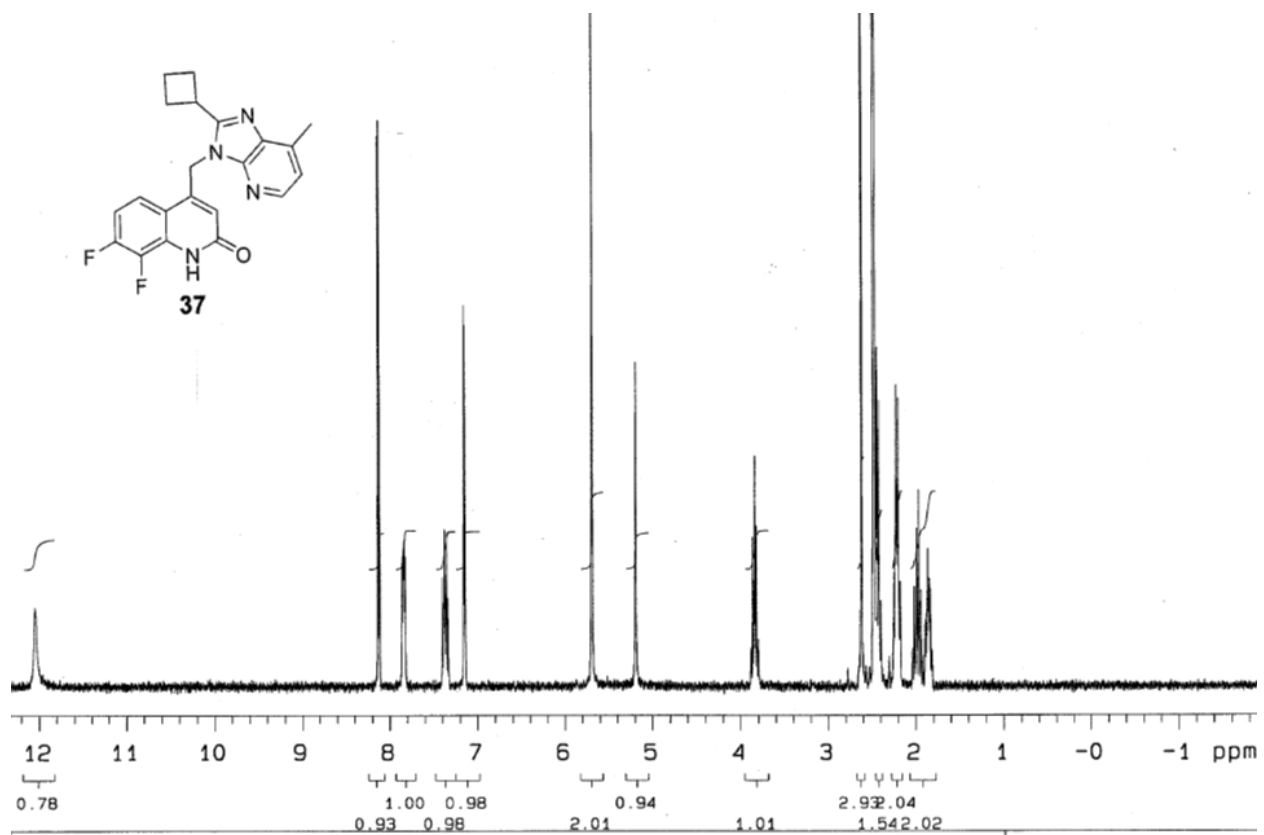
```

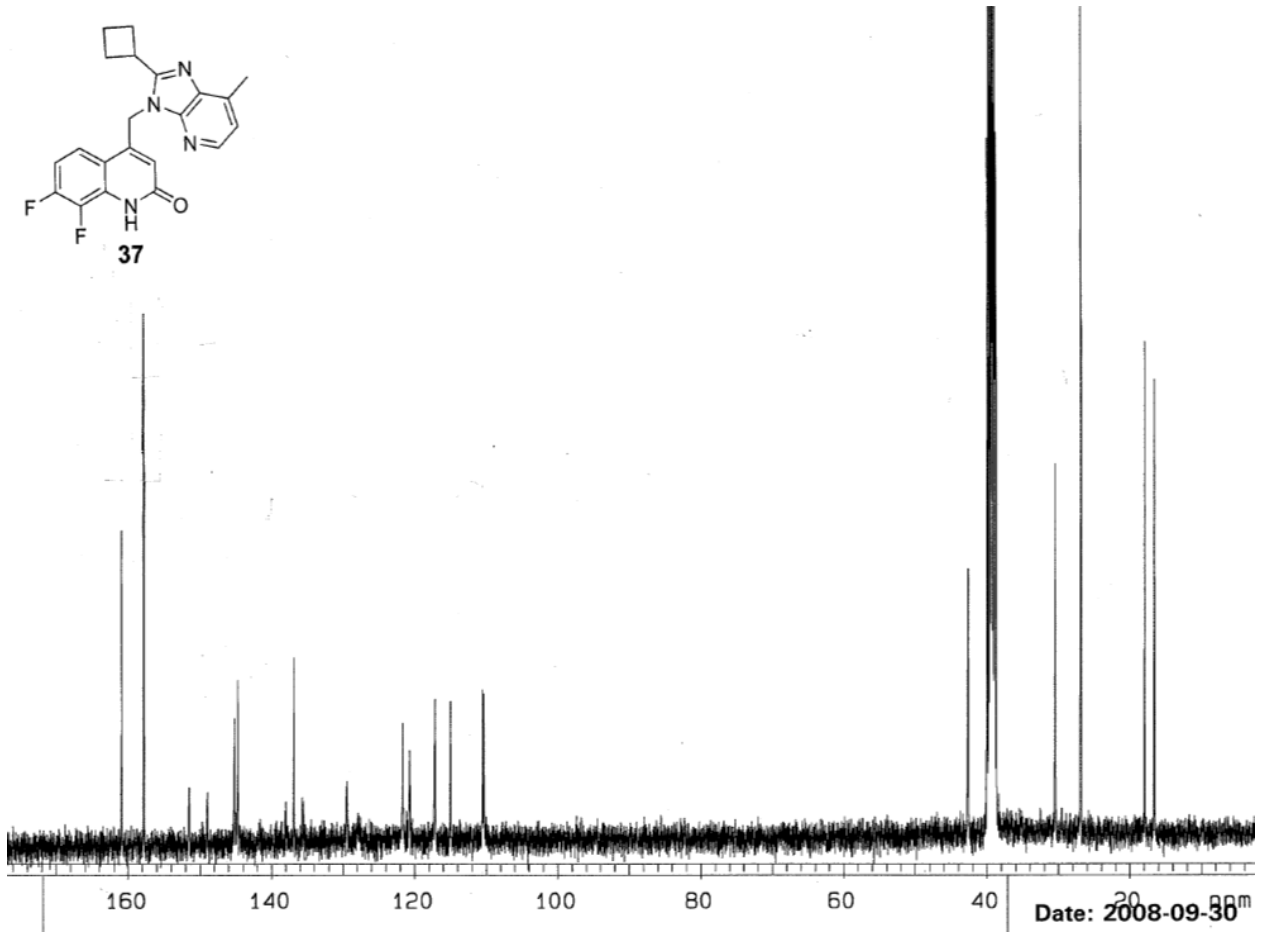
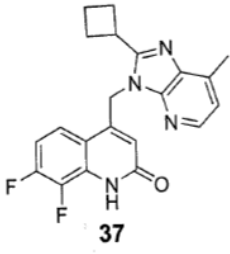
Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.348	BB	0.0519	8.16012	2.16666	0.3069
2	5.604	BB	0.1150	2650.51929	339.63382	99.6931

Totals : 2658.67941 341.80048

Compound 37: 4-((2-Cyclobutyl-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-7,8-difluoroquinolin-2(1H)-one

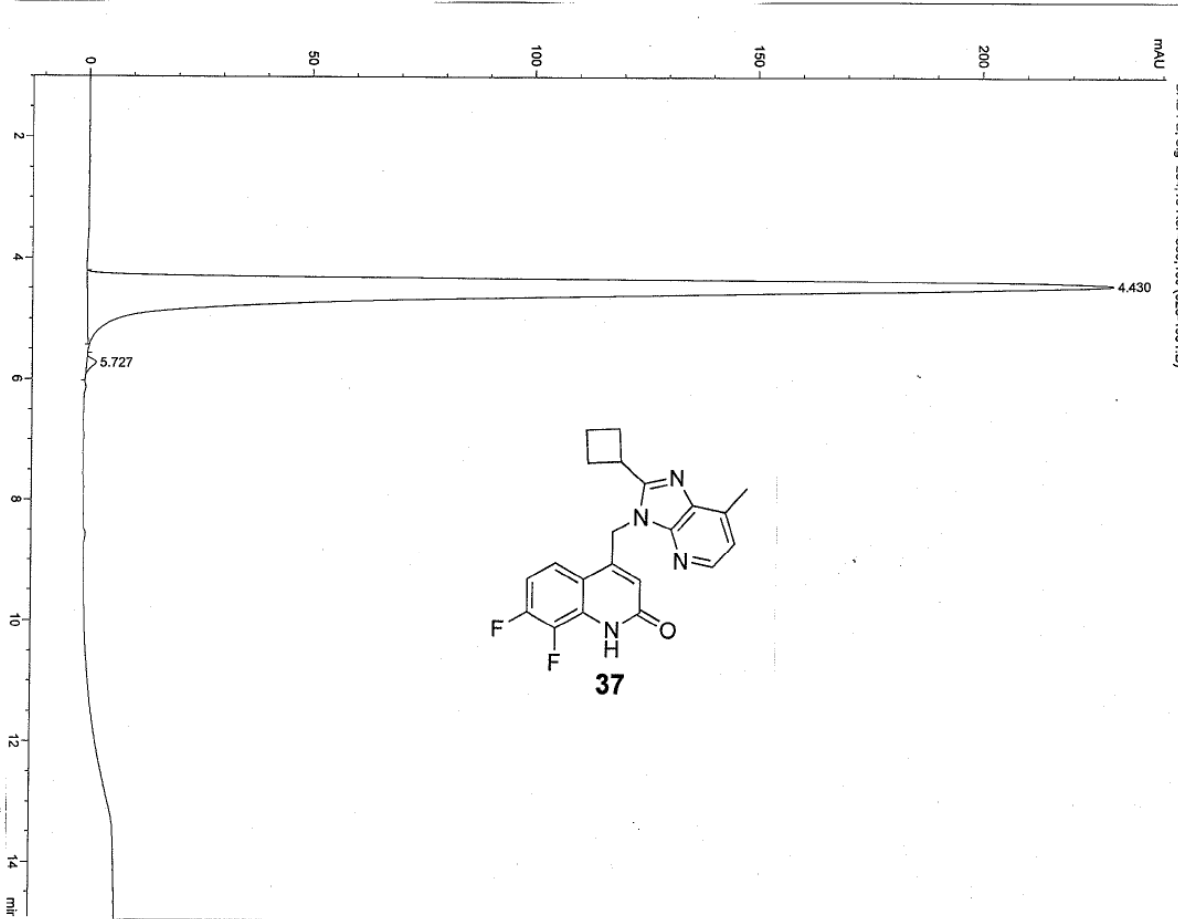




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=====
Injection Date   : 10/31/2008 12:33:05 PM      Seq. Line : 15
Sample Name     :                               Location  : Vial 26
Acq. Operator   :                               Inj       : 1
Acq. Instrument : Kalypsys                       Inj Volume: 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 10/31/2008 8:33:04 AM by 1
1%-95% AcCN in H2O, .05%TFA
=====

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Area Percent Report
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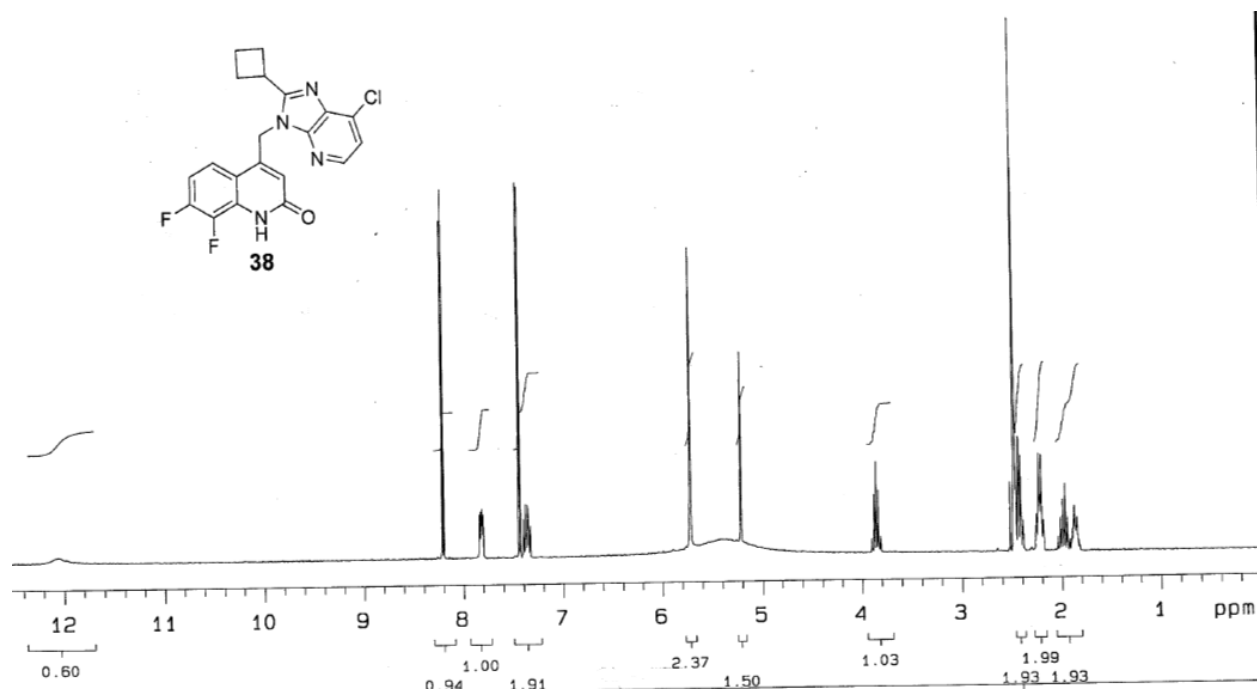
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

```

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.430	BB	0.2960	4365.72852	229.45972	99.5684
2	5.727	BB	0.1374	18.92327	2.09395	0.4316

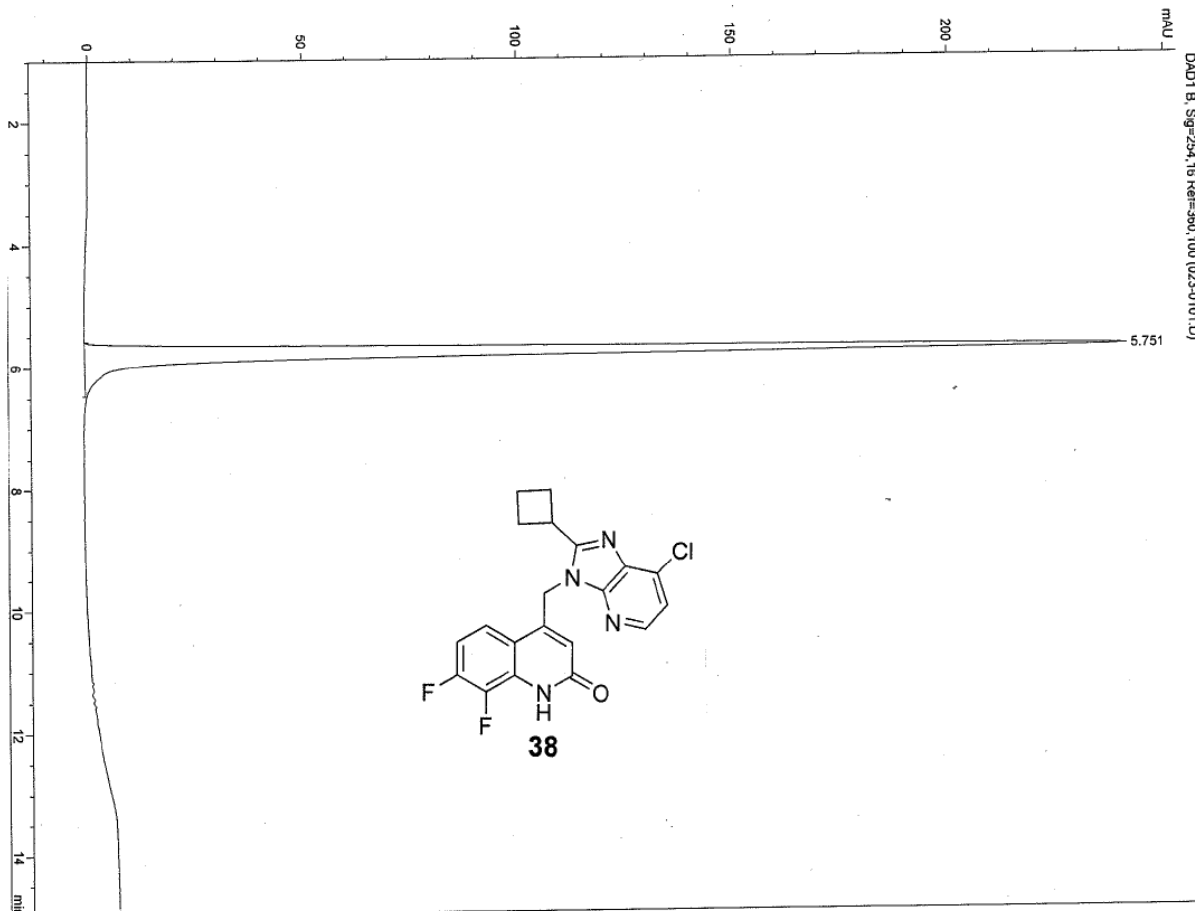
Compound 38: 4-((7-Chloro-2-cyclobutyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



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=====
Injection Date : 11/4/2008 3:36:10 PM      Seq. Line : 1
Sample Name    :                            Location  : Vial 23
Acq. Operator : 1                          Inj       : 1
Acq. Instrument : Kalypsys                  Inj Volume: 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/4/2008 2:57:25 PM by 1
1%-95% AcCN in H2O, .05%TFA
=====

```



Area Percent Report

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Sorted By      :      Signal
Multiplier    :      1.0000
Dilution      :      1.0000
Use Multiplier & Dilution Factor with ISTDs

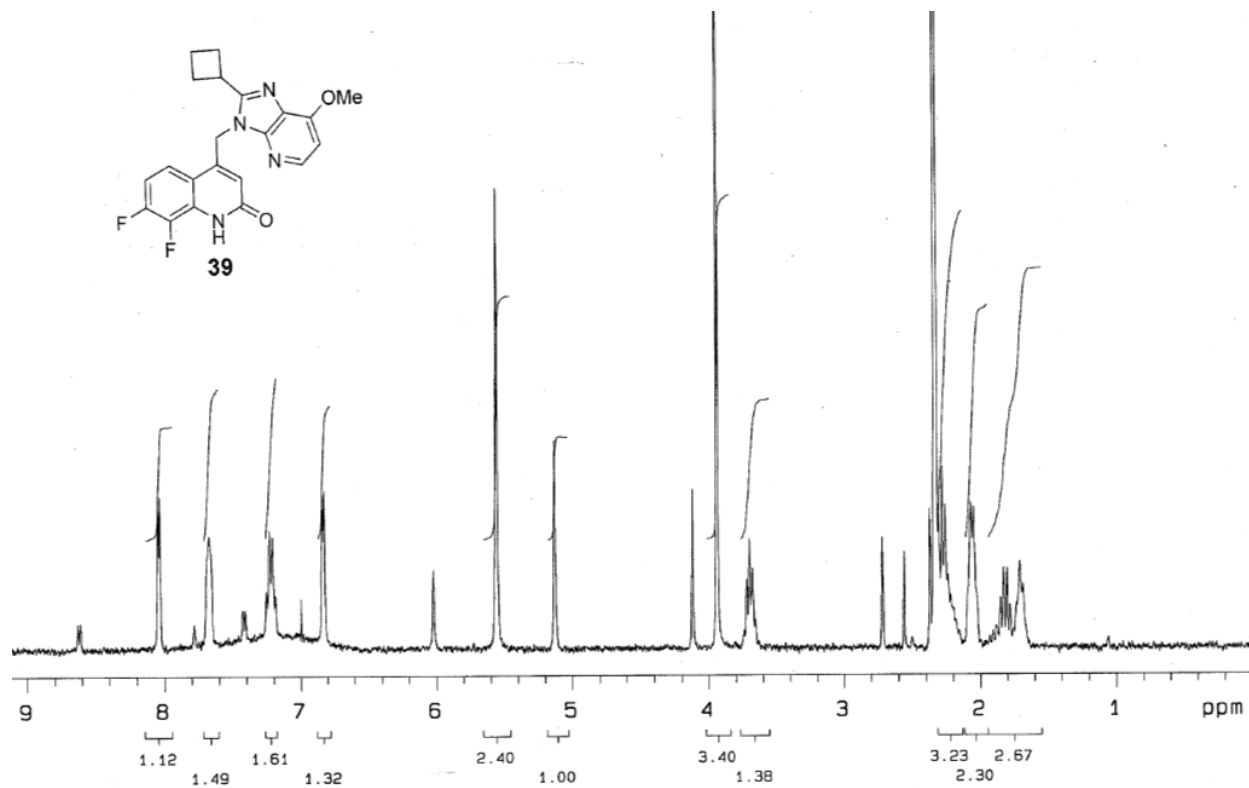
```

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.751	BB	0.1473	2350.13354	242.09079	100.0000

Totals : 2350.13354 242.09079

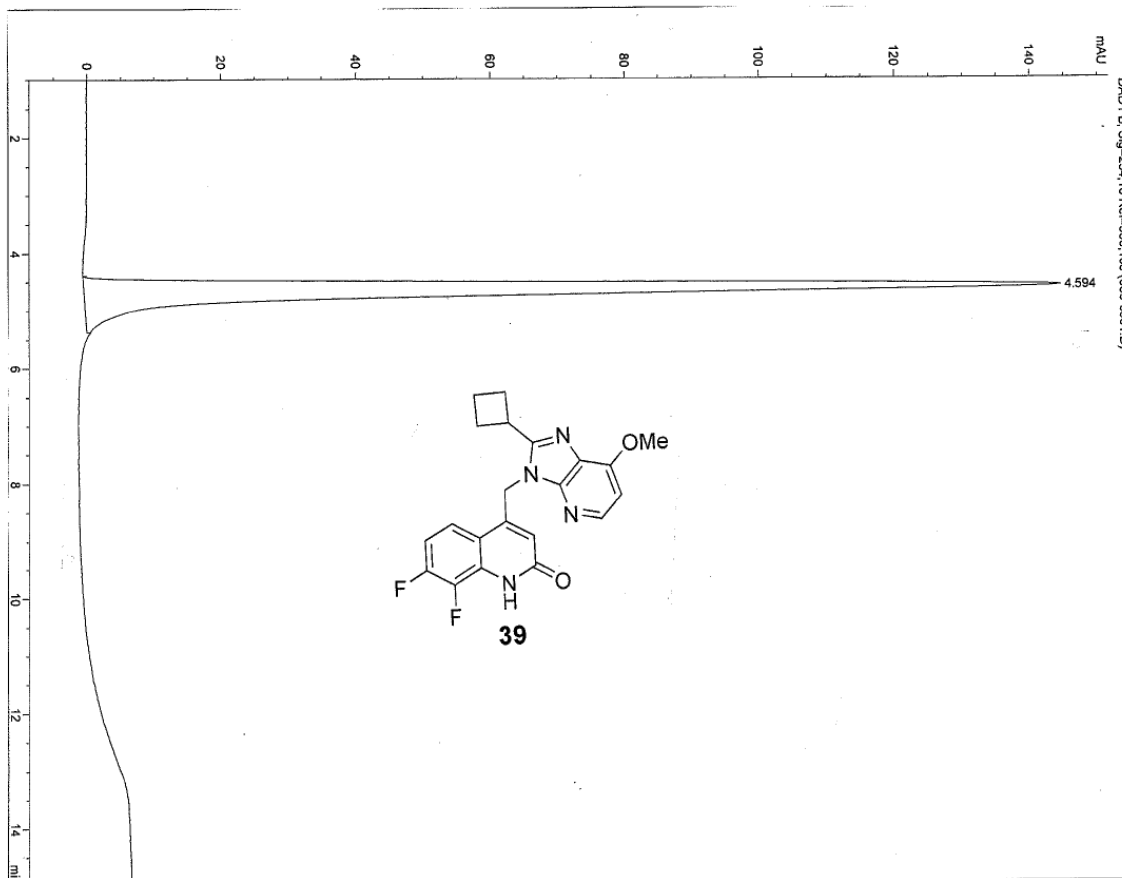
Compound 39: 4-((2-Cyclobutyl-7-methoxy-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



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=====
Injection Date : 11/3/2008 11:29:44 AM      Seq. Line : 5
Sample Name    :                               Location  : Vial 39
Acq. Operator  :                               Inj      : 1
Acq. Instrument : Kalypsys                     Inj Volume: 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/3/2008 10:20:09 AM by 1
1%-95% AcCN in H2O, .05%TFA
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                          Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution      :      1.0000
Use Multiplier & Dilution Factor with ISTDs

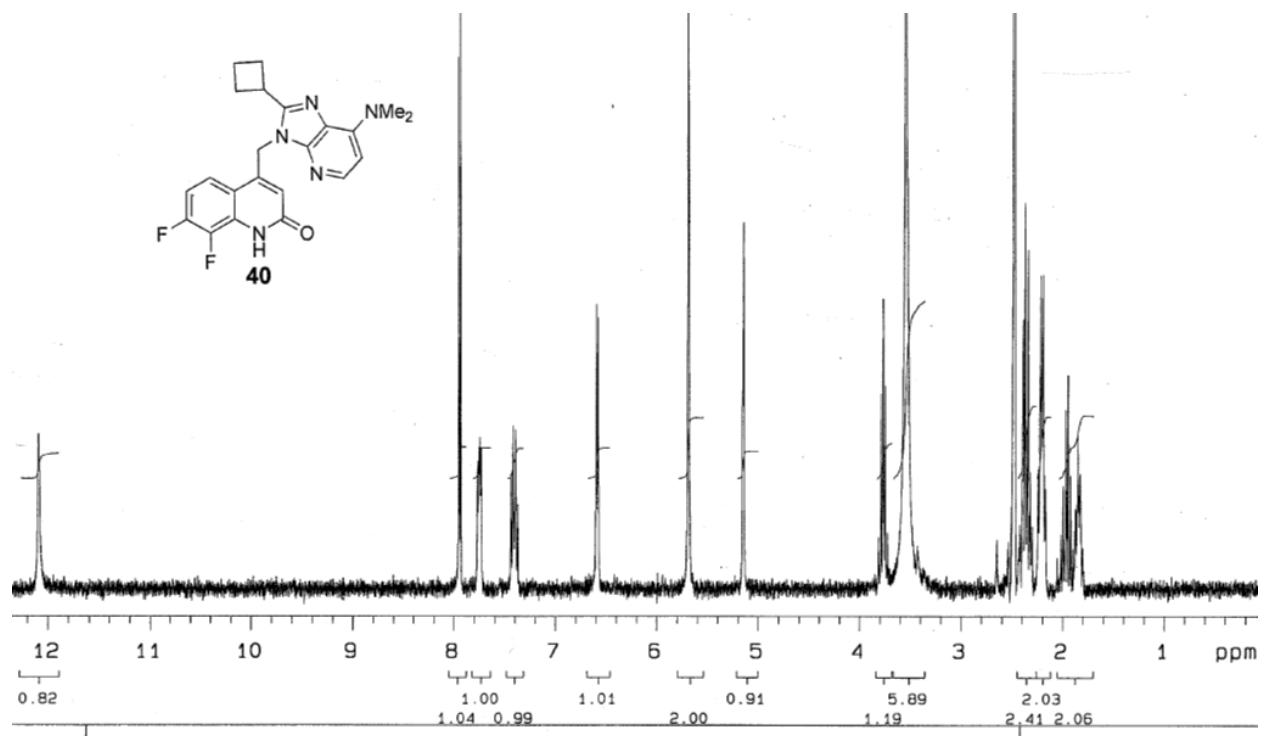
```

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.594	BB	0.2196	2109.58154	145.08345	100.0000

```
Totals :                2109.58154  145.08345
```

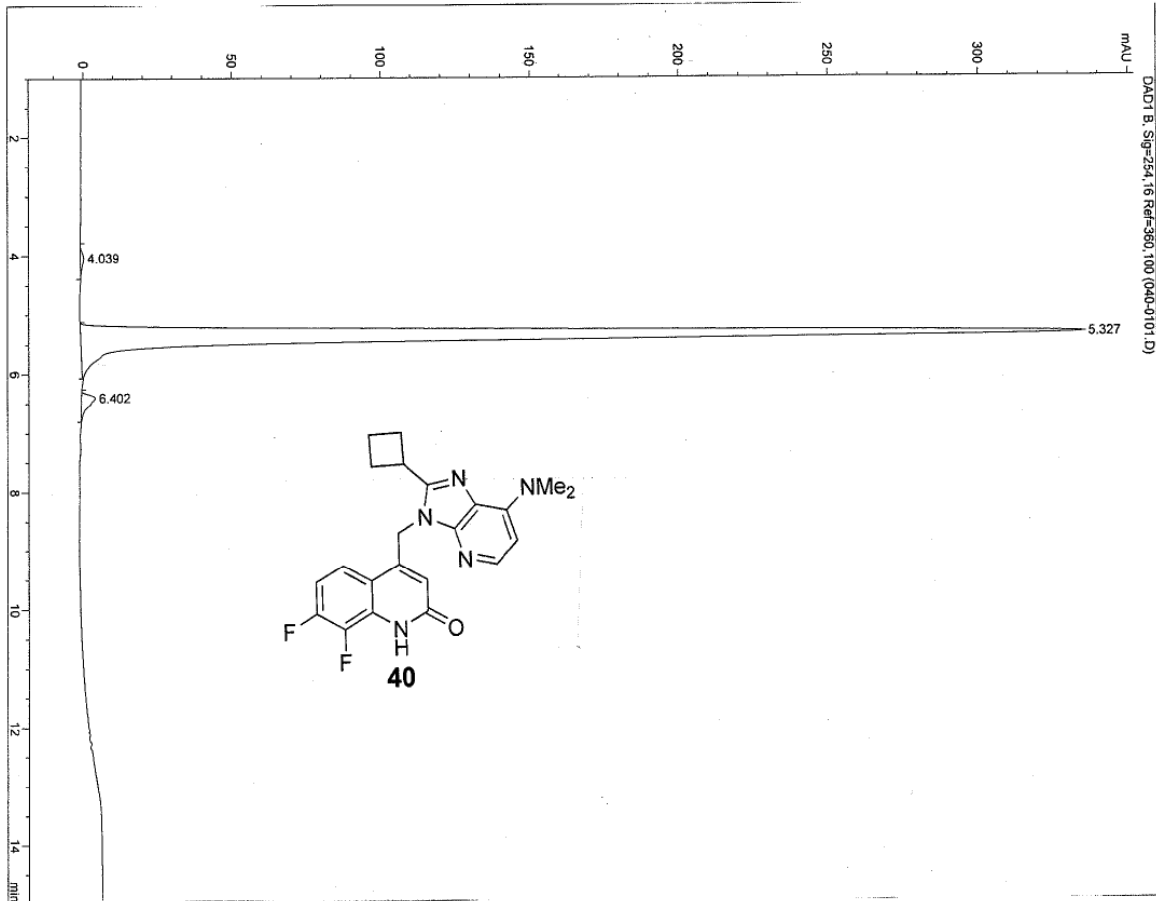
Compound 40: 4-((2-Cyclobutyl-7-(dimethylamino)-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



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=====
Injection Date   : 11/5/2008 11:43:41 AM      Seq. Line   : 1
Sample Name     :                               Location    : Vial 40
Acq. Operator   :                               Inj         : 1
Acq. Instrument : Kalypsys                       Inj Volume  : 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 11/5/2008 11:42:33 AM by 1
1%-95% AcCN in H2O, .05%TFA
=====

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Area Percent Report

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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

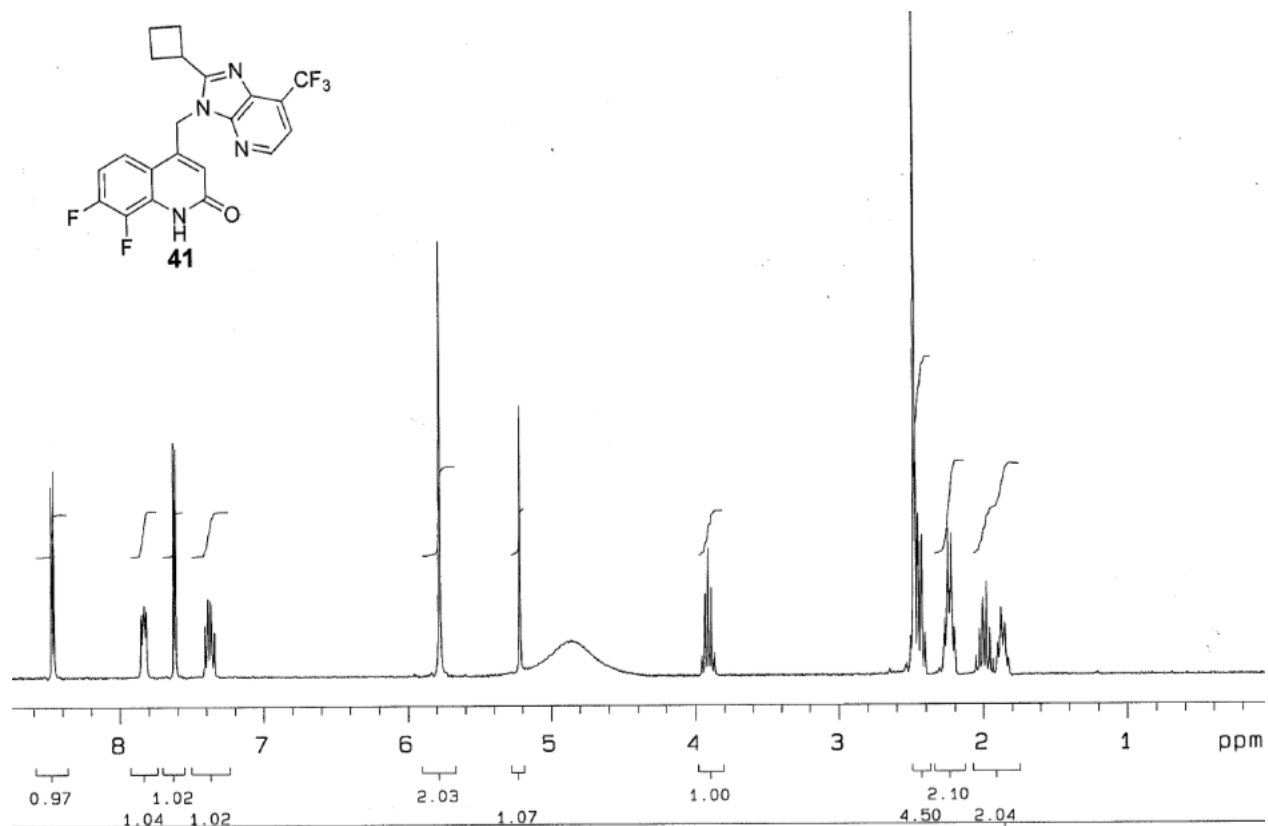
```

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.039	BB	0.2293	21.06616	1.22064	0.5365
2	5.327	BB	0.1774	3844.78589	336.37585	97.9161
3	6.402	BB	0.1825	60.76111	4.64924	1.5474

Totals : 3926.61316 342.24573

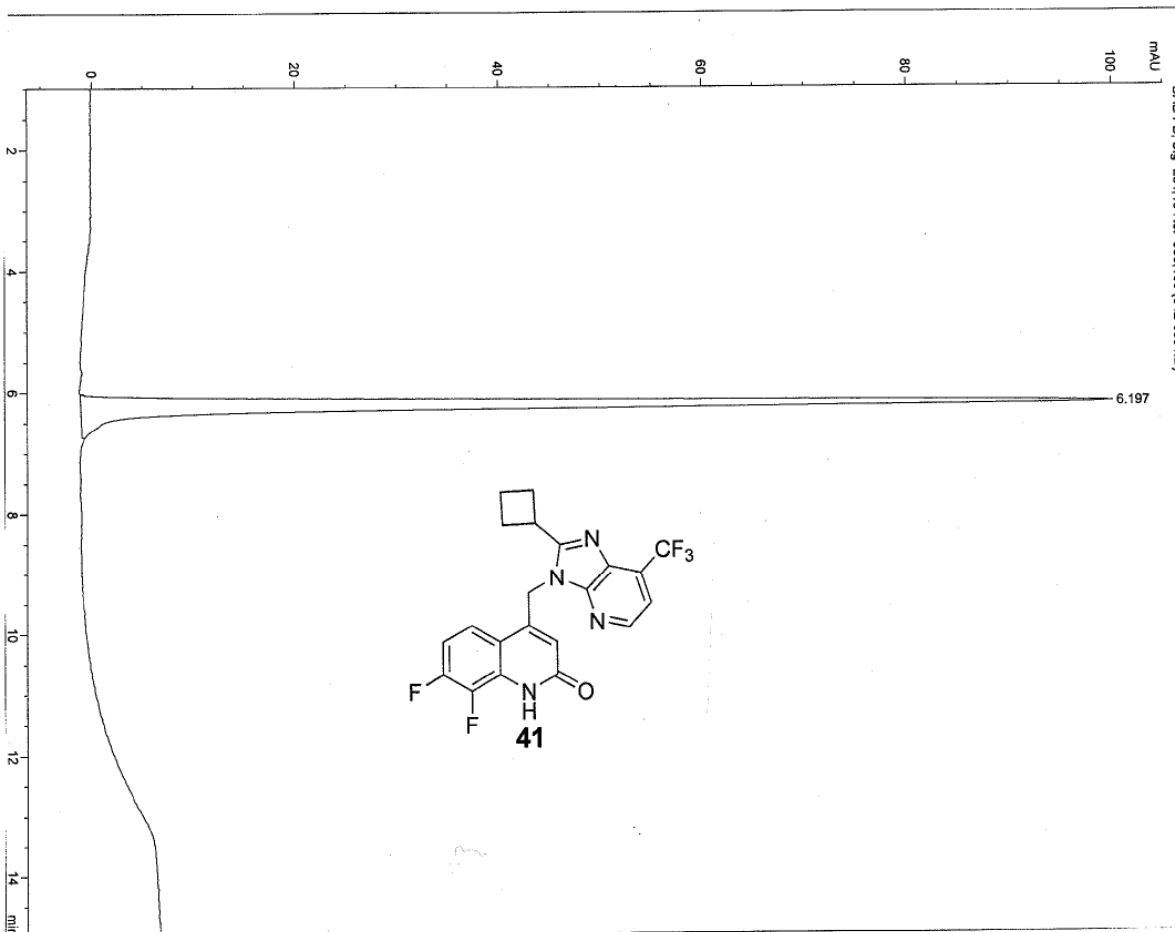
Compound 41: 4-((2-Cyclobutyl-7-(trifluoromethyl)-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



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=====
Injection Date : 11/3/2008 12:21:02 PM      Seq. Line : 8
Sample Name   :                               Location  : Vial 42
Acq. Operator :                               Inj      : 1
Acq. Instrument :                             Inj Volume: 5 µl
Sequence File : C:\CHEM32\1\SEQUENCE\DEF LC2.S
Method       : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed : 11/3/2008 10:20:09 AM by 1
1%-95% AcCN in H2O, .05%TFA
=====

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Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

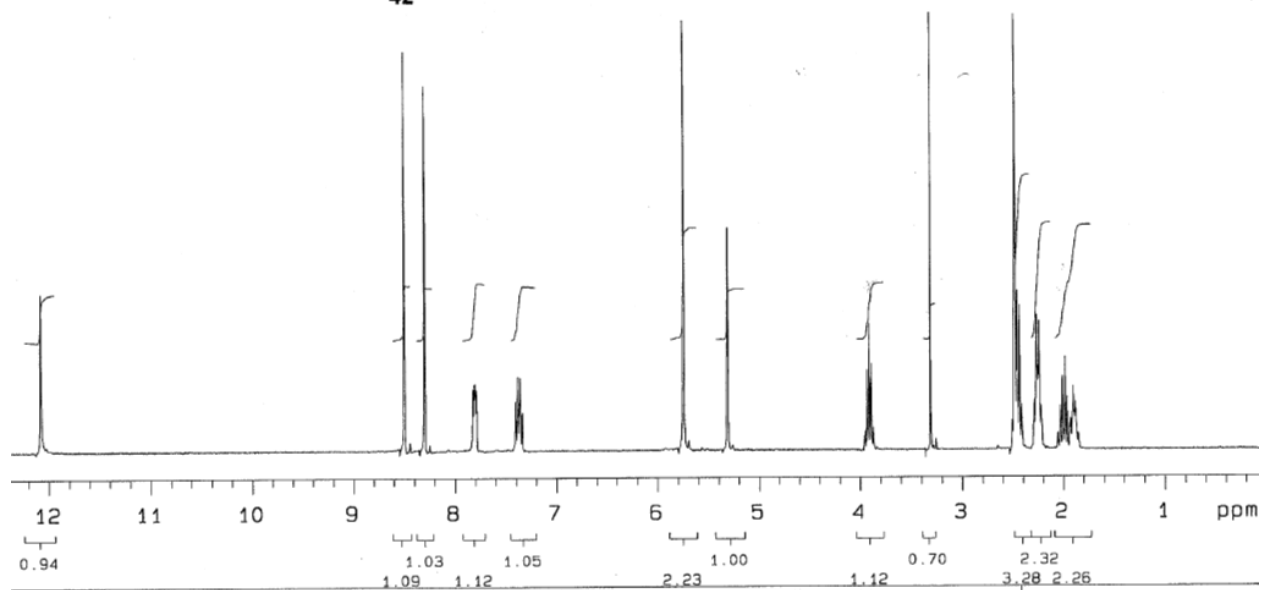
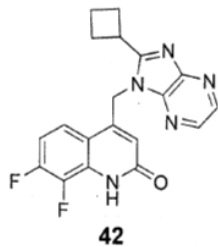
```

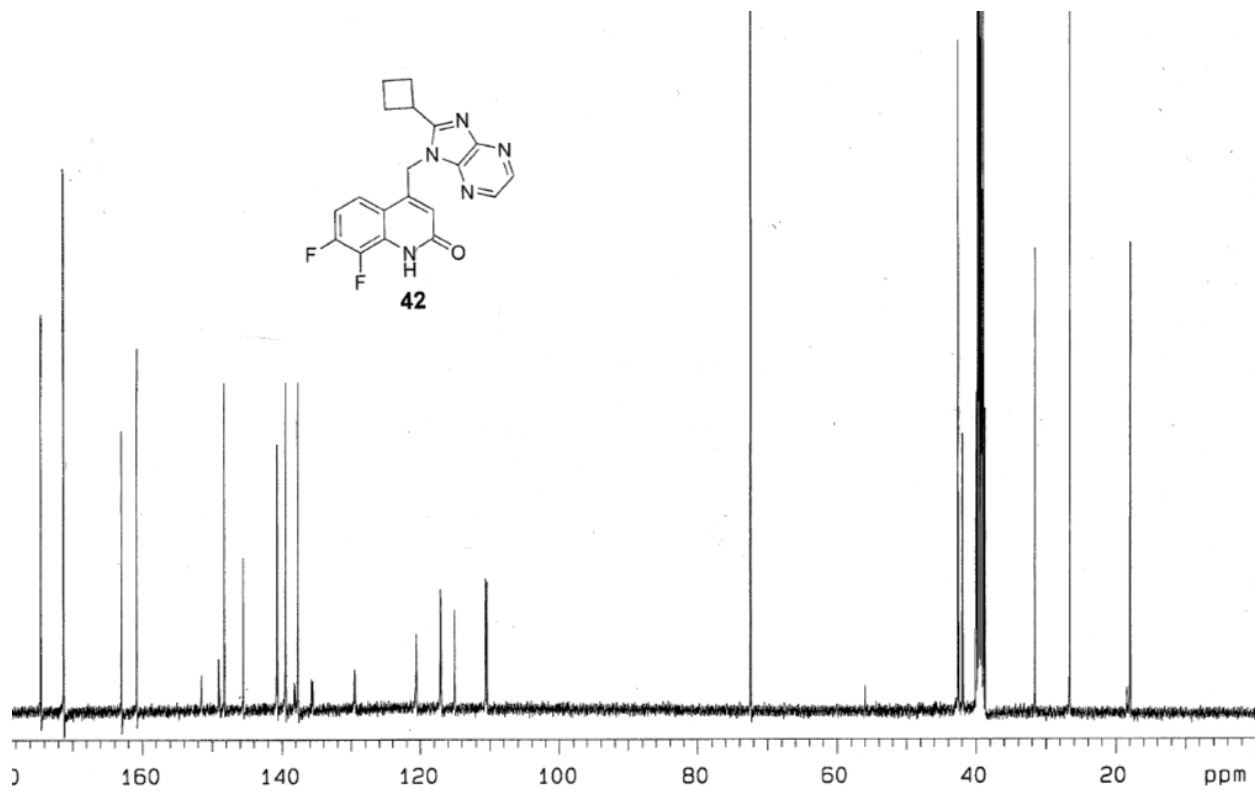
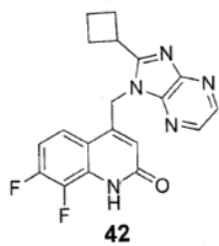
Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.197	BB	0.1476	968.25500	101.23230	100.0000

Totals : 968.25500 101.23230

Compound 42: 4-((2-Cyclobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-one

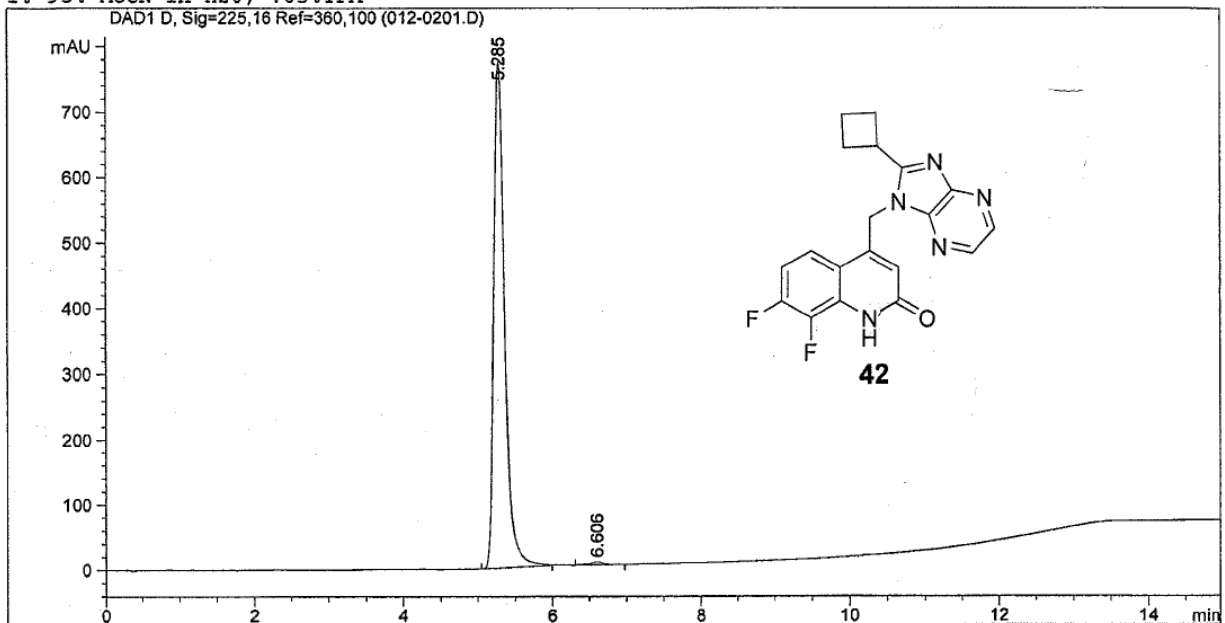




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=====
Injection Date   : 3/10/2008 10:30:31 AM      Seq. Line   :    2
Sample Name     :                               Location    : Vial 12
Acq. Operator   :                               Inj         :    1
Acq. Instrument : Kalypsys                      Inj Volume  : 2 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 3/10/2008 10:11:32 AM by 14
1%-95% AcCN in H2O, .05%TFA
=====

```



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Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

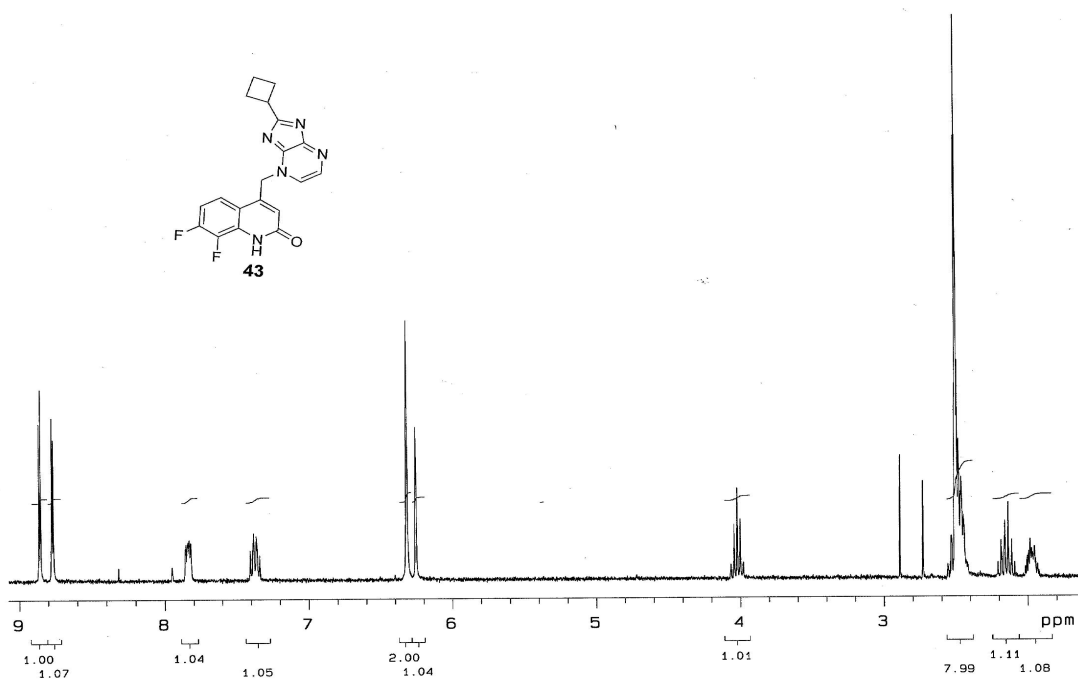
```

Signal 1: DAD1 D, Sig=225,16 Ref=360,100

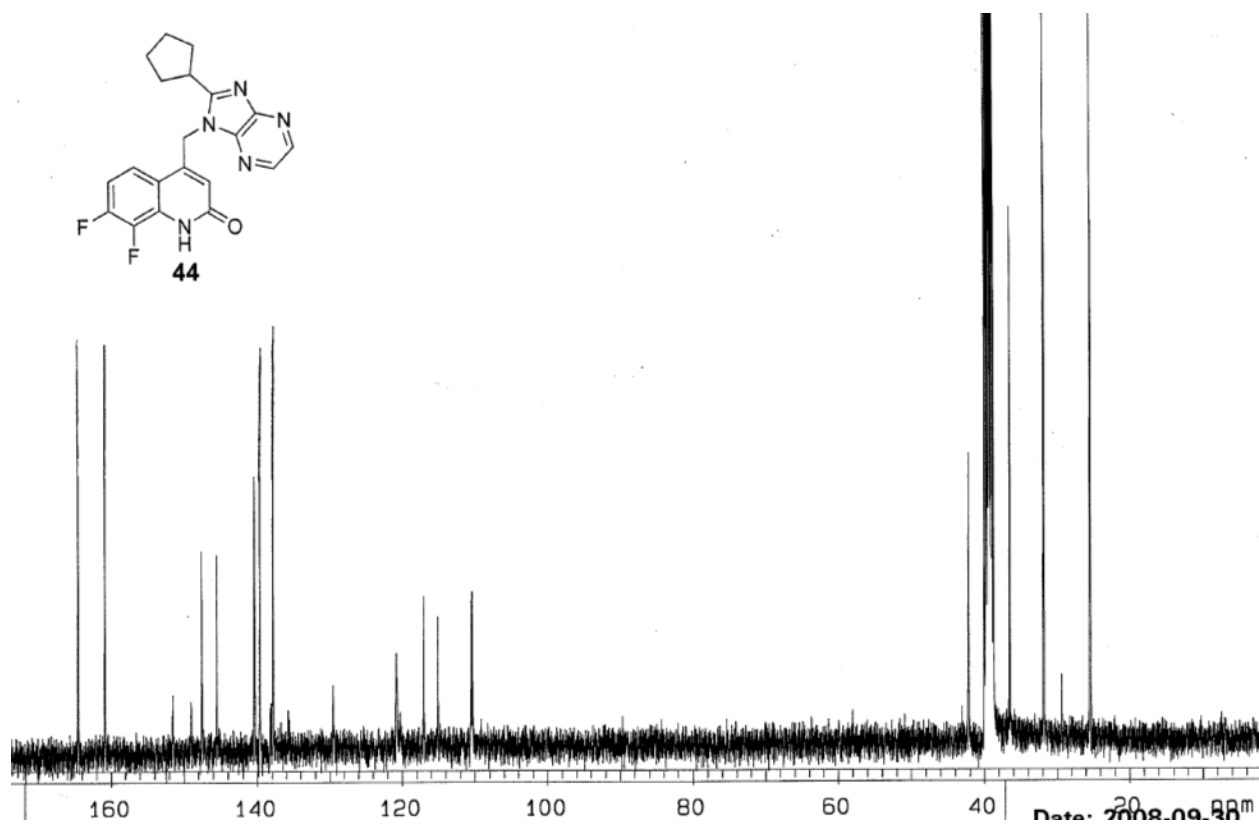
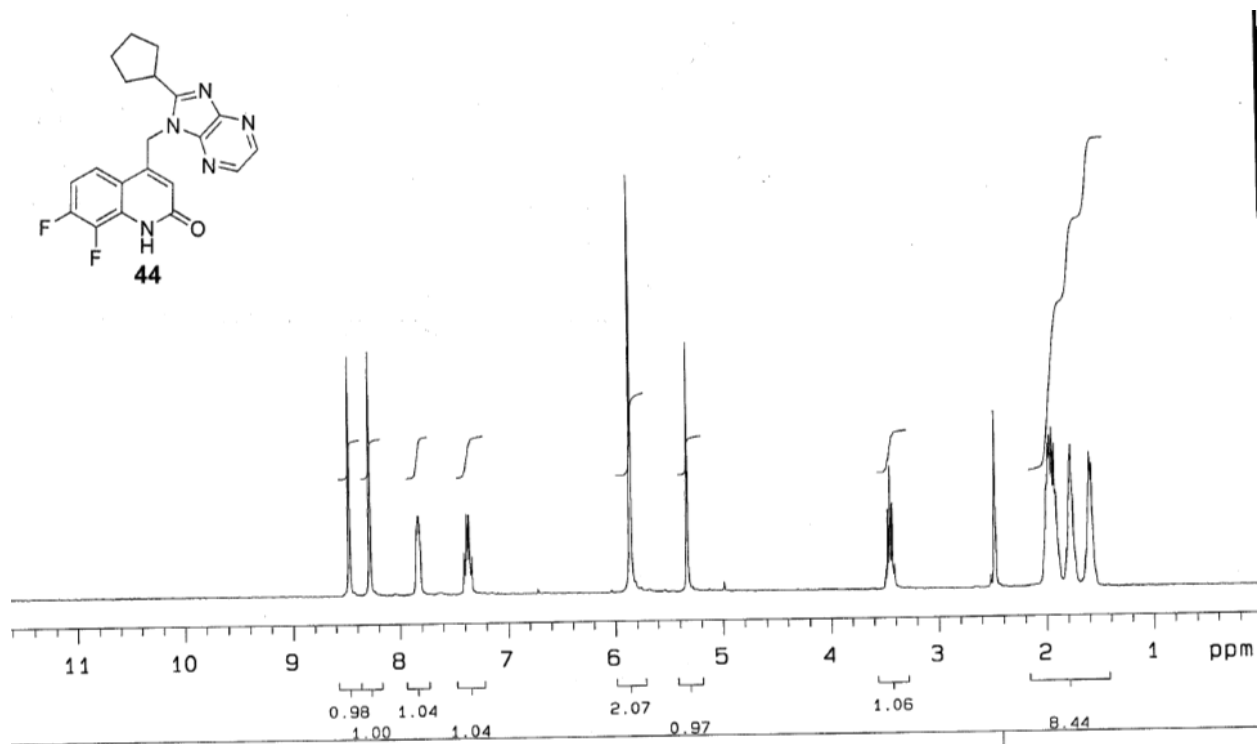
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.285	BB	0.1560	7818.64844	772.71240	99.2497
2	6.606	BB	0.1793	59.10473	4.81049	0.7503

Totals : 7877.75317 777.52290

Compound 43: 4-((2-cyclobutyl-4H-imidazo[4,5-b]pyrazin-4-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



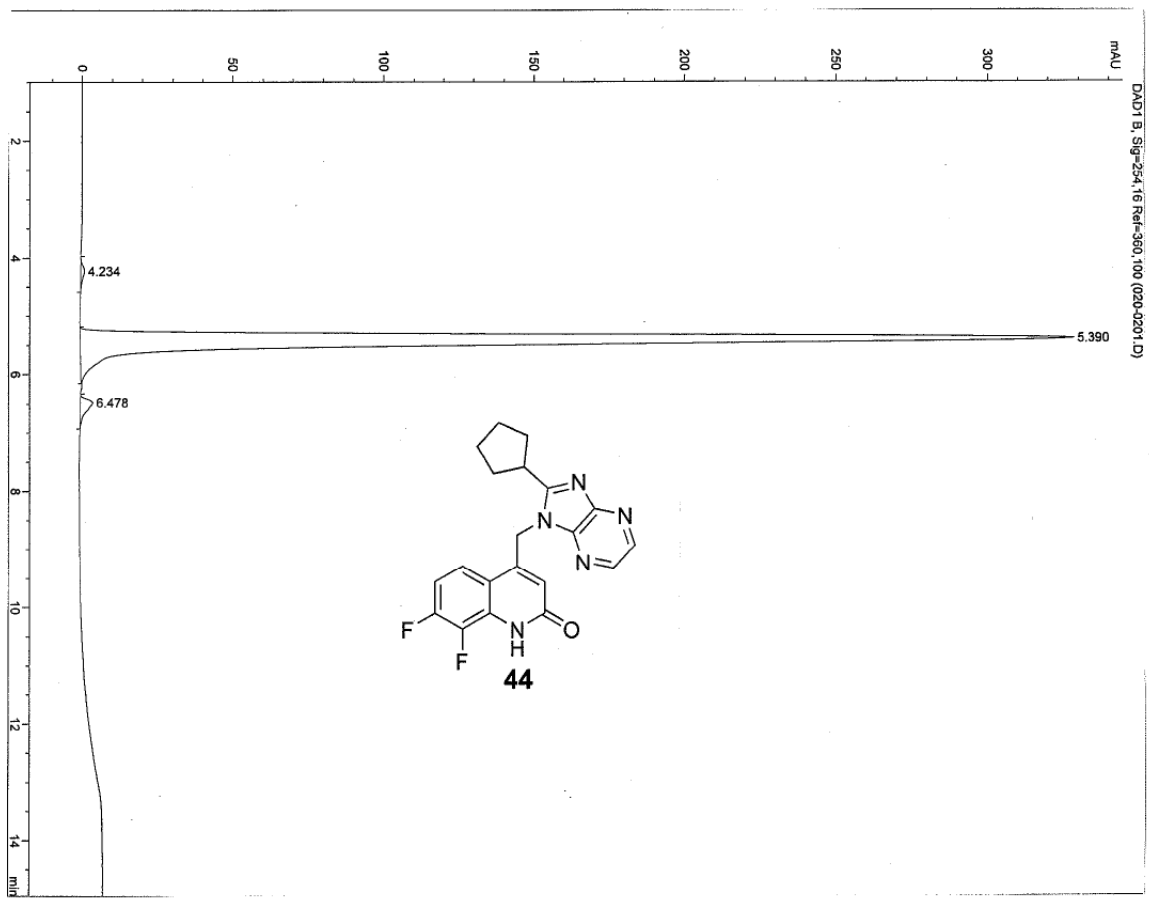
Compound 44: 4-((2-Cyclopentyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-one



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=====
Injection Date   : 11/4/2008 3:15:41 PM           Seq. Line :    2
Sample Name     :                               Location  : Vial 20
Acq. Operator   :                               Inj       :    1
Acq. Instrument : Kalypsys                       Inj Volume: 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 11/4/2008 2:57:25 PM by 1
1%-95% AcCN in H2O, .05%TFA
=====

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Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution      :      1.0000
Use Multiplier & Dilution Factor with ISTDs

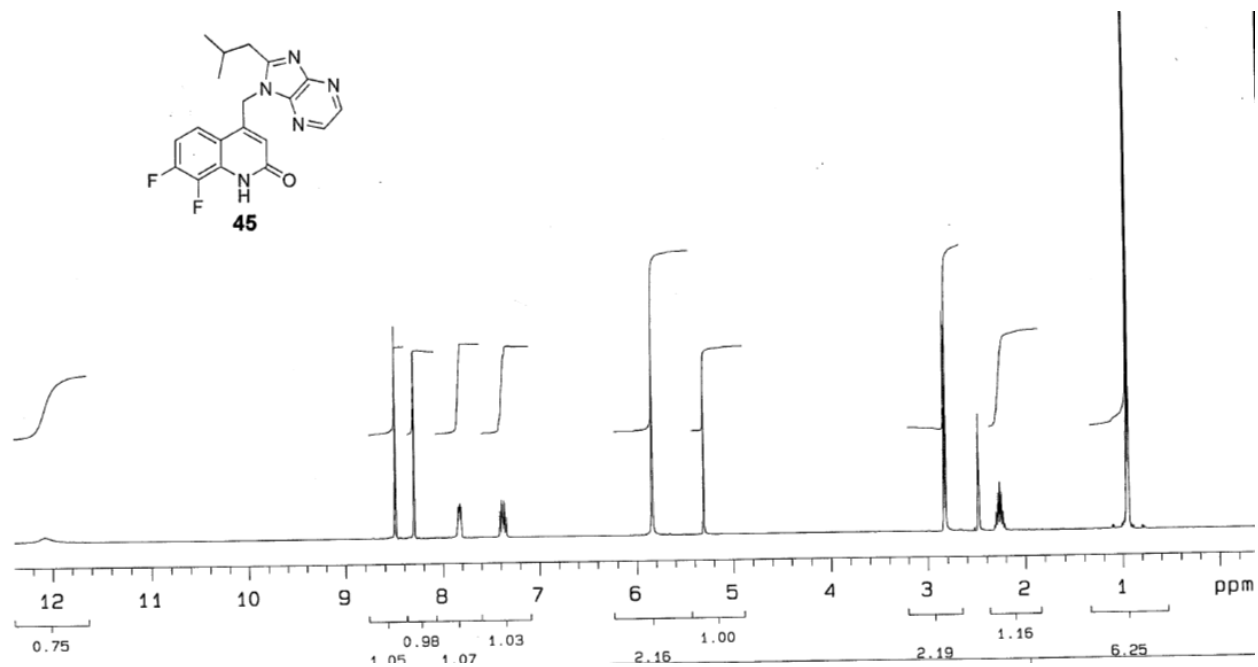
```

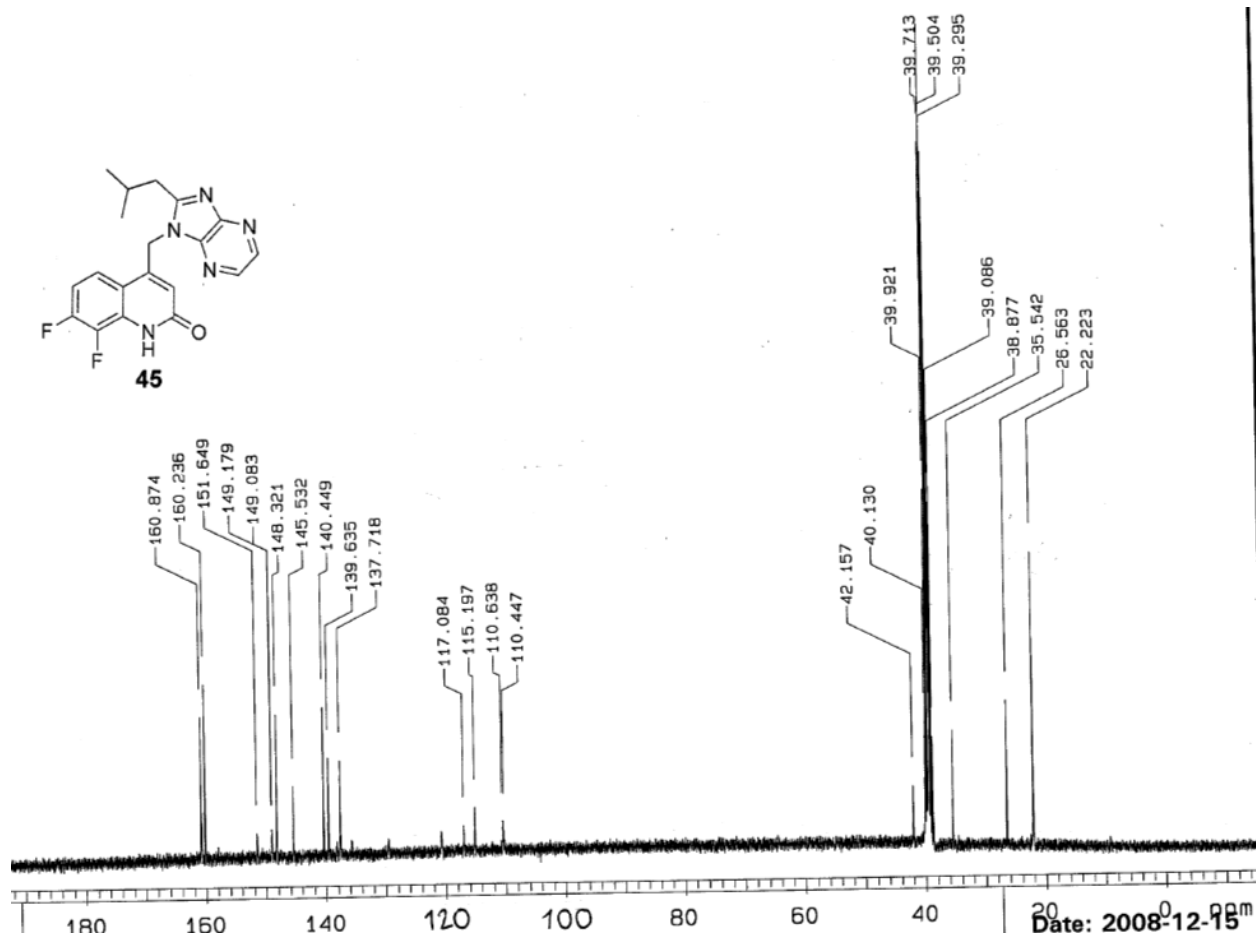
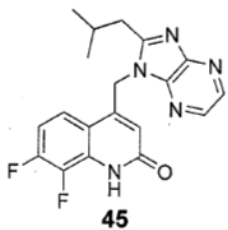
Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.234	BB	0.2404	20.97917	1.29881	0.5460
2	5.390	BB	0.1774	3761.93994	328.93811	97.9077
3	6.478	BB	0.1993	59.41542	4.14415	1.5463

Totals : 3842.33453 334.38107

Compound 45: 7,8-Difluoro-4-((2-isobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)quinolin-2(1H)-one

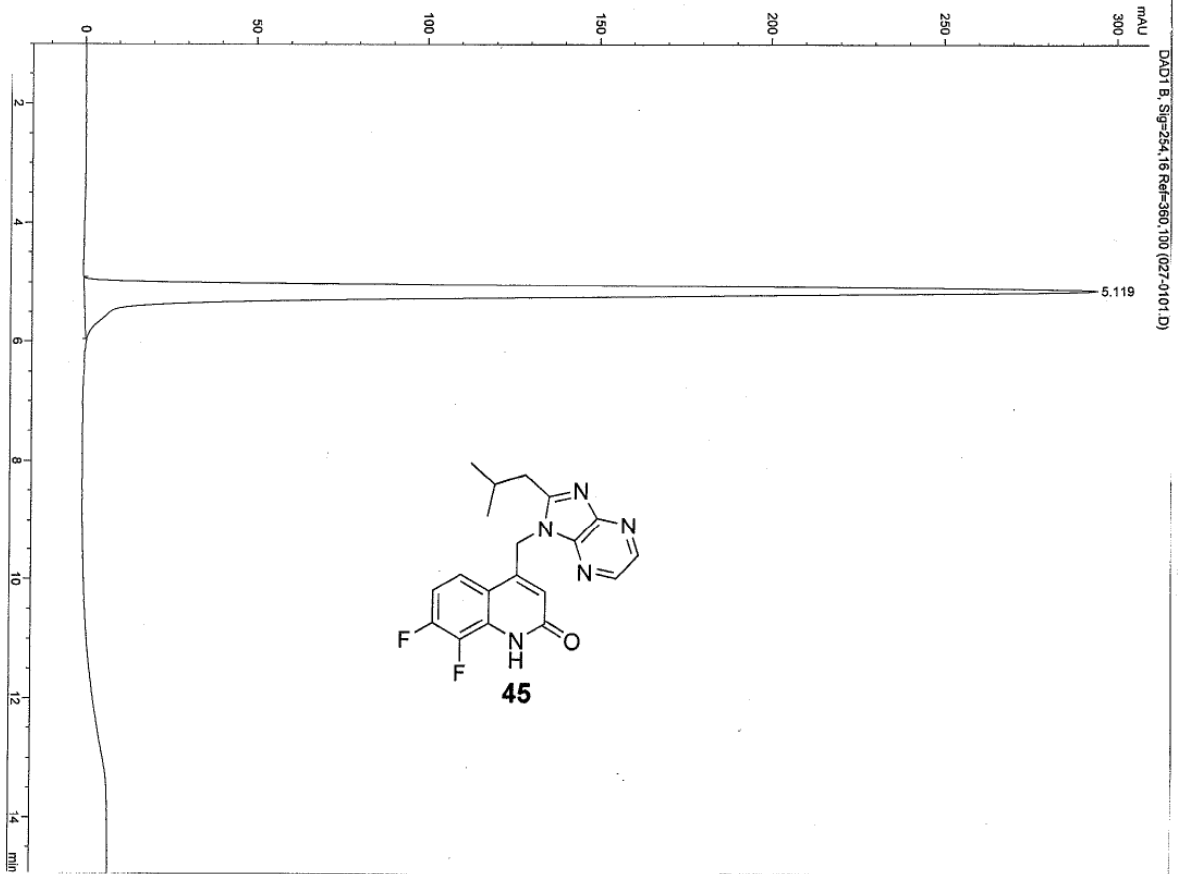




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=====
Injection Date : 11/4/2008 2:58:32 PM      Seq. Line : 1
Sample Name    :                            Location  : Vial 27
Acq. Operator  : 1                          Inj       : 1
Acq. Instrument : Kalypsys                   Inj Volume: 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/4/2008 2:57:25 PM by 1
1%-95% AccN in H2O, .05%TFA
=====

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Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

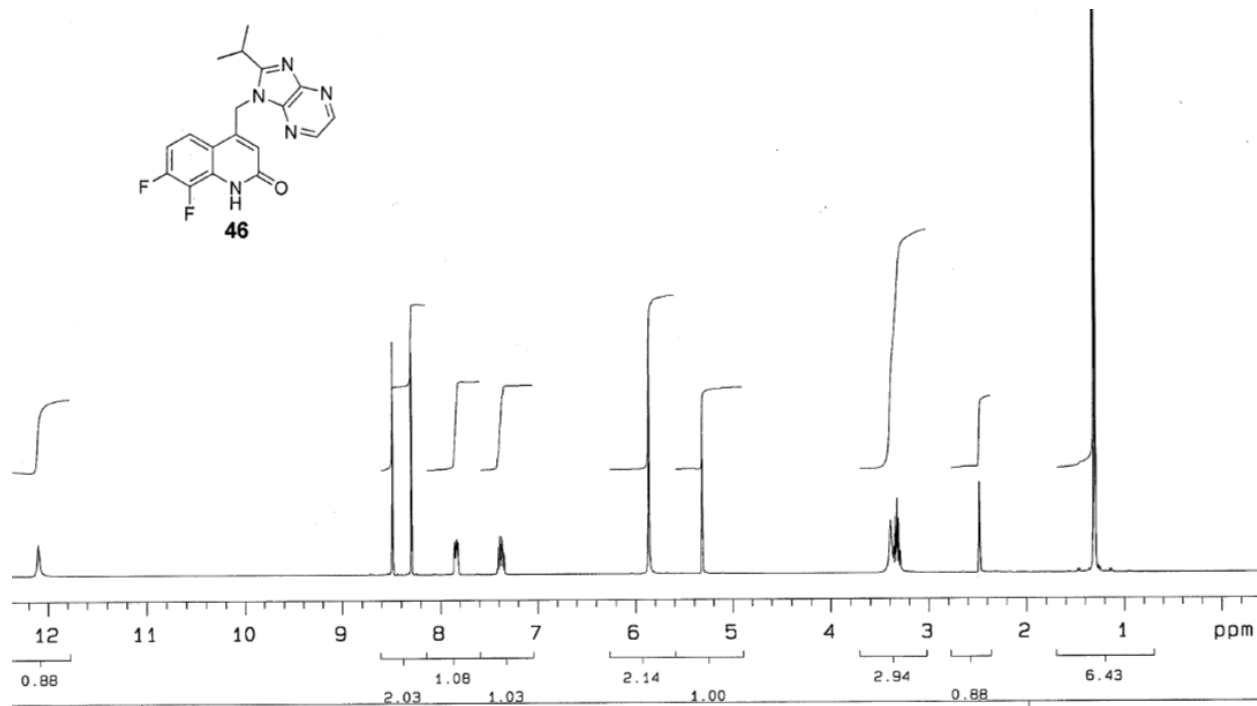
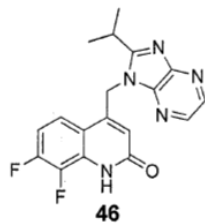
```

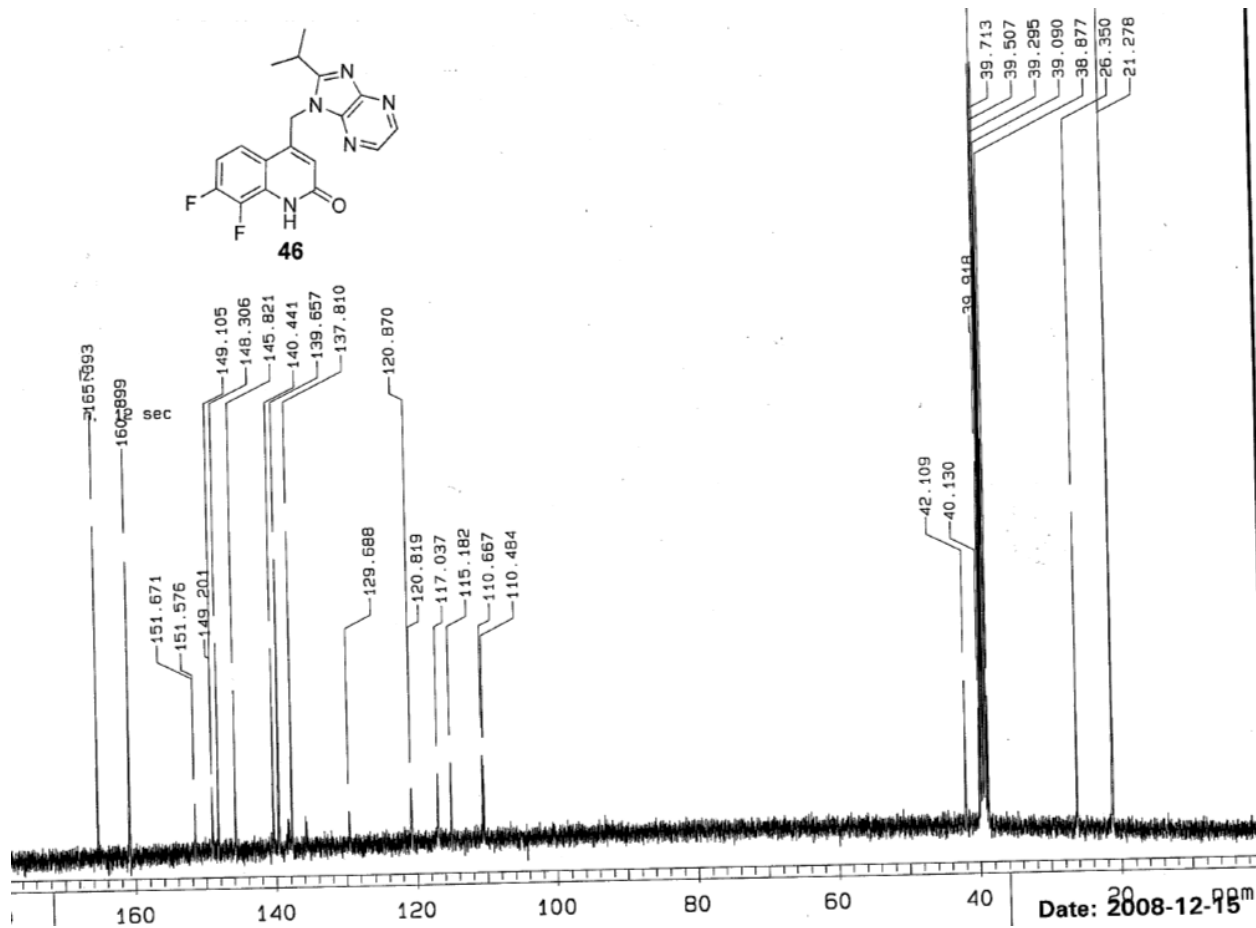
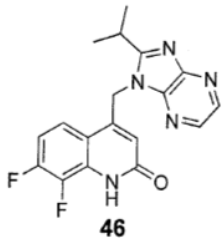
Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.119	BB	0.2026	3803.02246	294.55106	100.0000

Totals : 3803.02246 294.55106

Compound 46: 7,8-Difluoro-4-((2-isopropyl-1*H*-imidazo[4,5-*b*]pyrazin-1-yl)methyl)quinolin-2(1*H*)-one

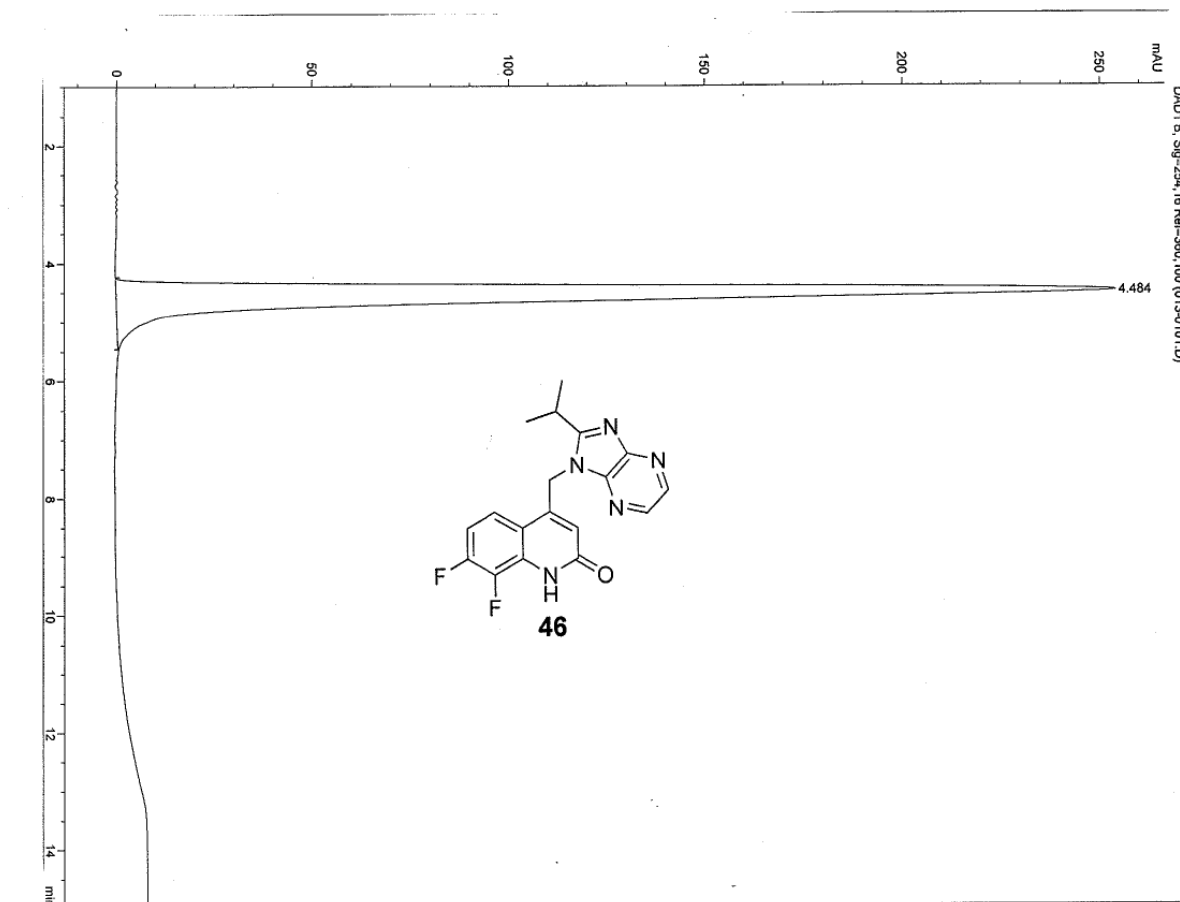




```

=====
Injection Date : 11/6/2008 5:30:07 PM      Seq. Line : 1
Sample Name    :                            Location  : Vial 13
Acq. Operator  : 1                          Inj       : 1
Acq. Instrument : Kalypsys                   Inj Volume: 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method         : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/6/2008 5:28:59 PM by 1
1%-95% AcCN in H2O, .05%TFA
=====

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Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

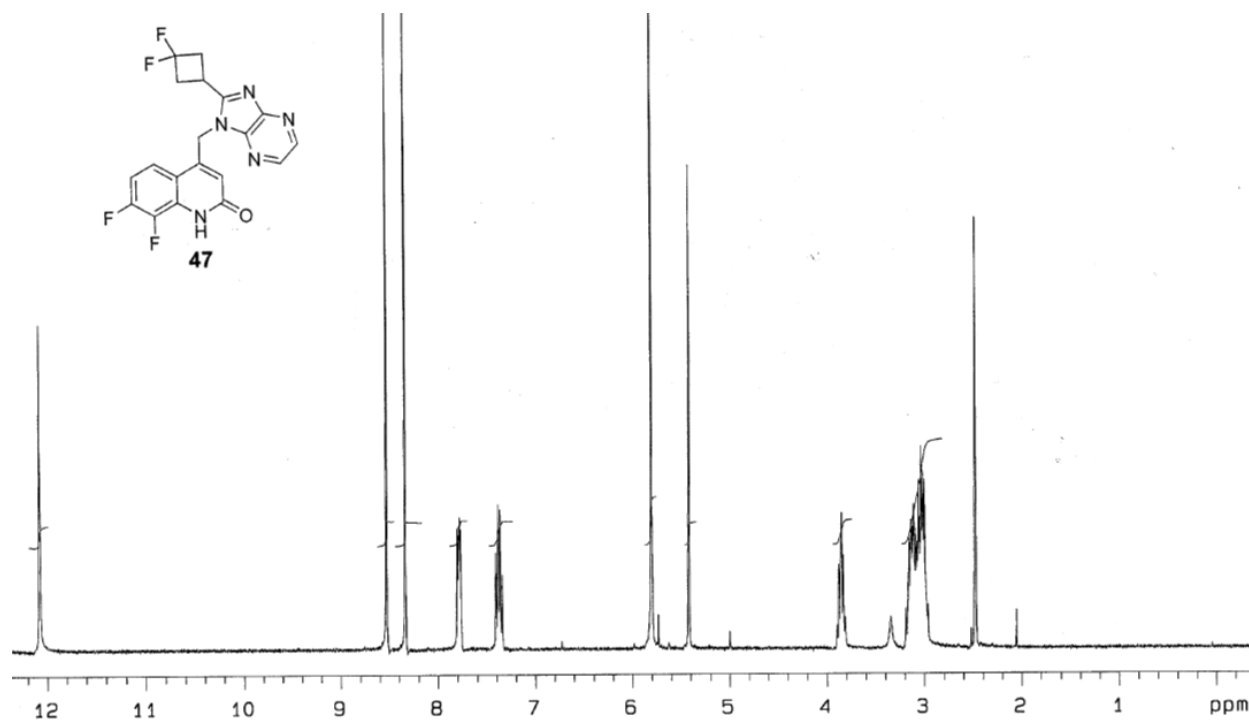
```

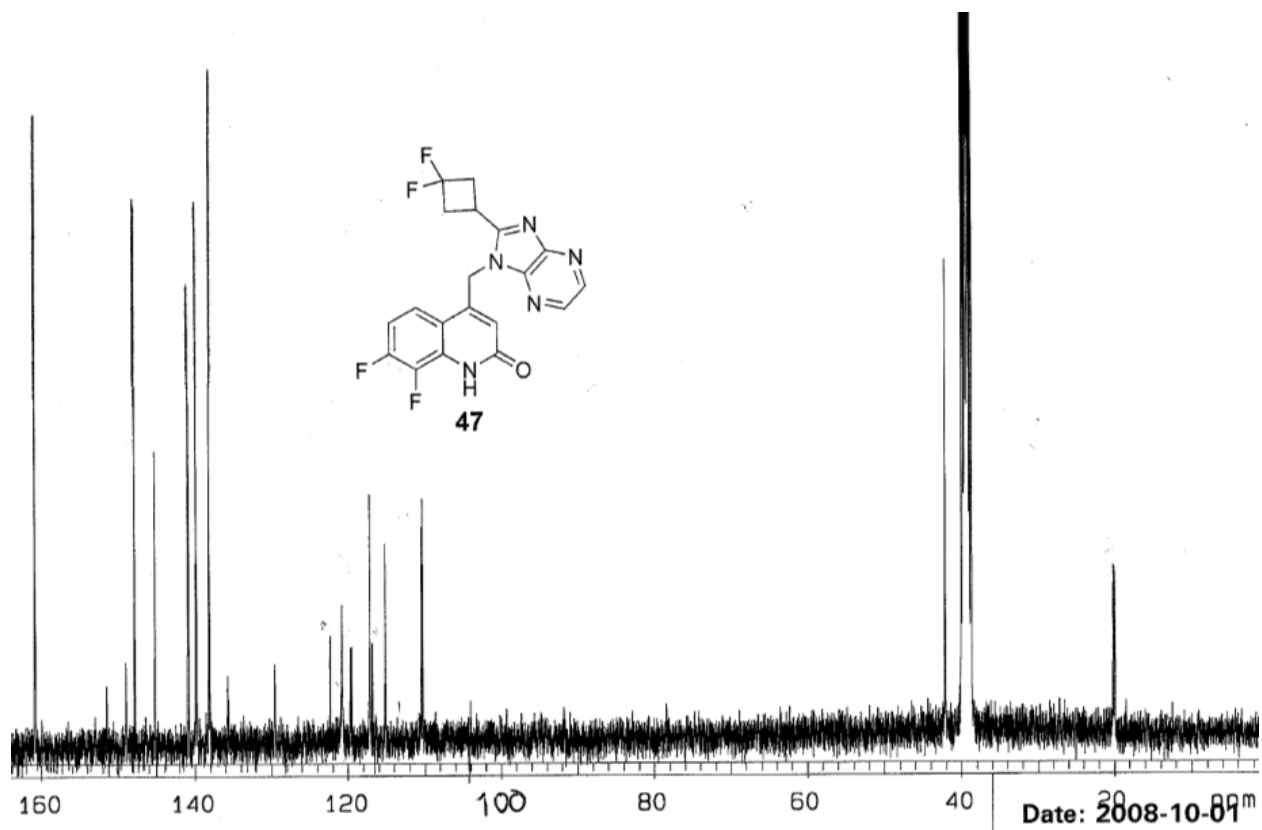
Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.484	BB	0.2648	4374.00977	254.10667	100.0000

Totals : 4374.00977 254.10667

Compound 47: 4-((2-(3,3-Difluorocyclobutyl)-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroquinolin-2(1H)-one

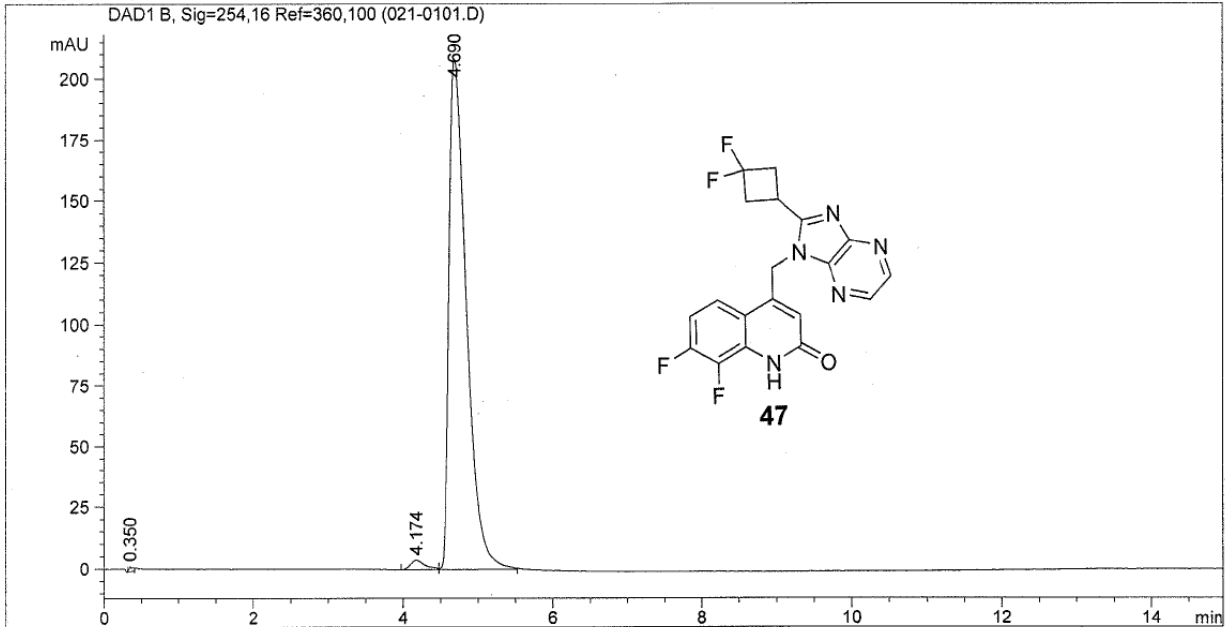




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=====
Injection Date   : 3/25/2009 4:20:35 PM      Seq. Line   : 1
Sample Name     : klyp720                    Location    : Vial 21
Acq. Operator   : 1                          Inj         : 1
Acq. Instrument : Kalypsys                    Inj Volume  : 5 µl
Sequence File   : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method          : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed    : 3/25/2009 3:10:25 PM by 1
1%-95% AcCN in H2O

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                          Area Percent Report
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Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs

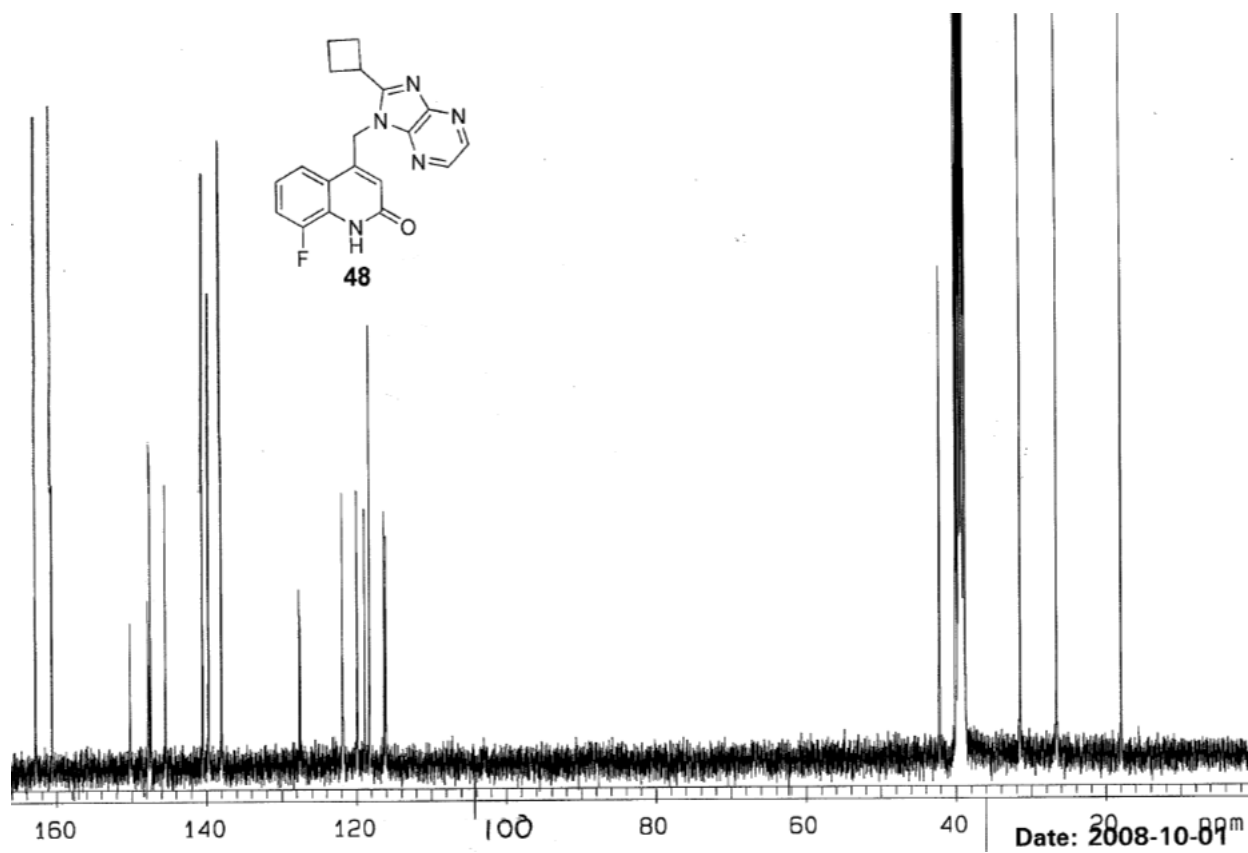
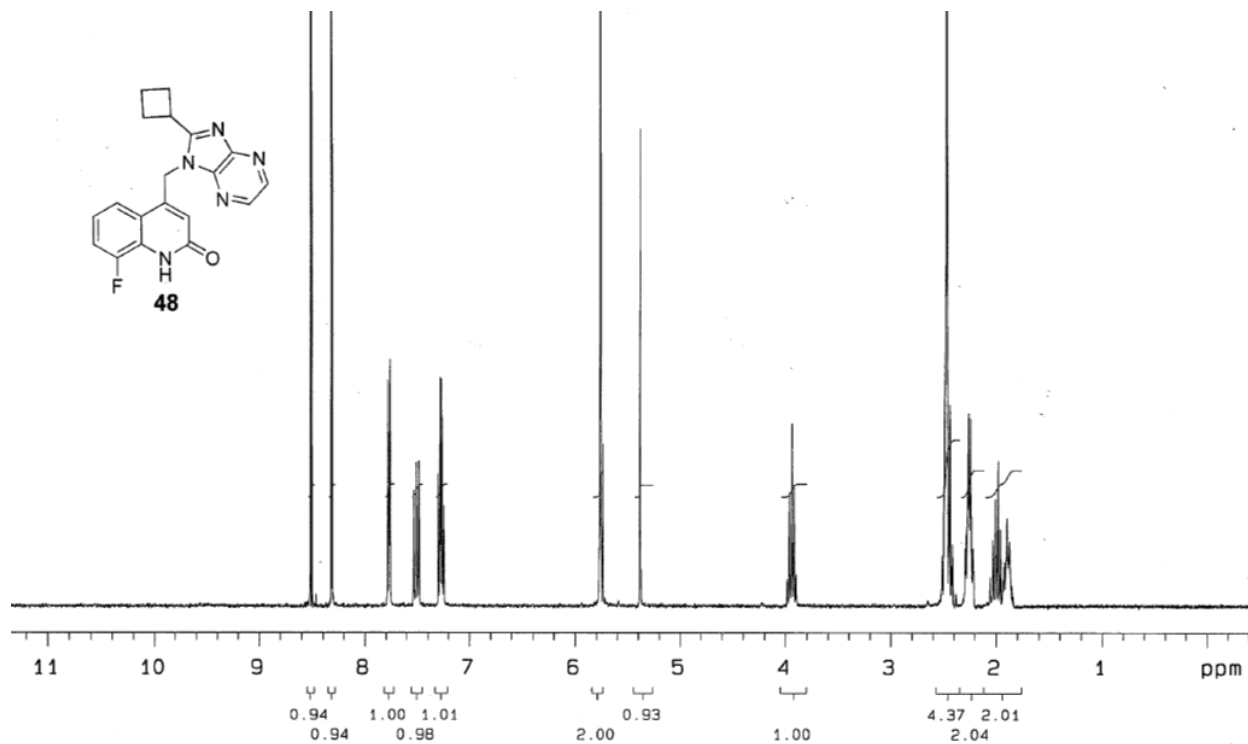
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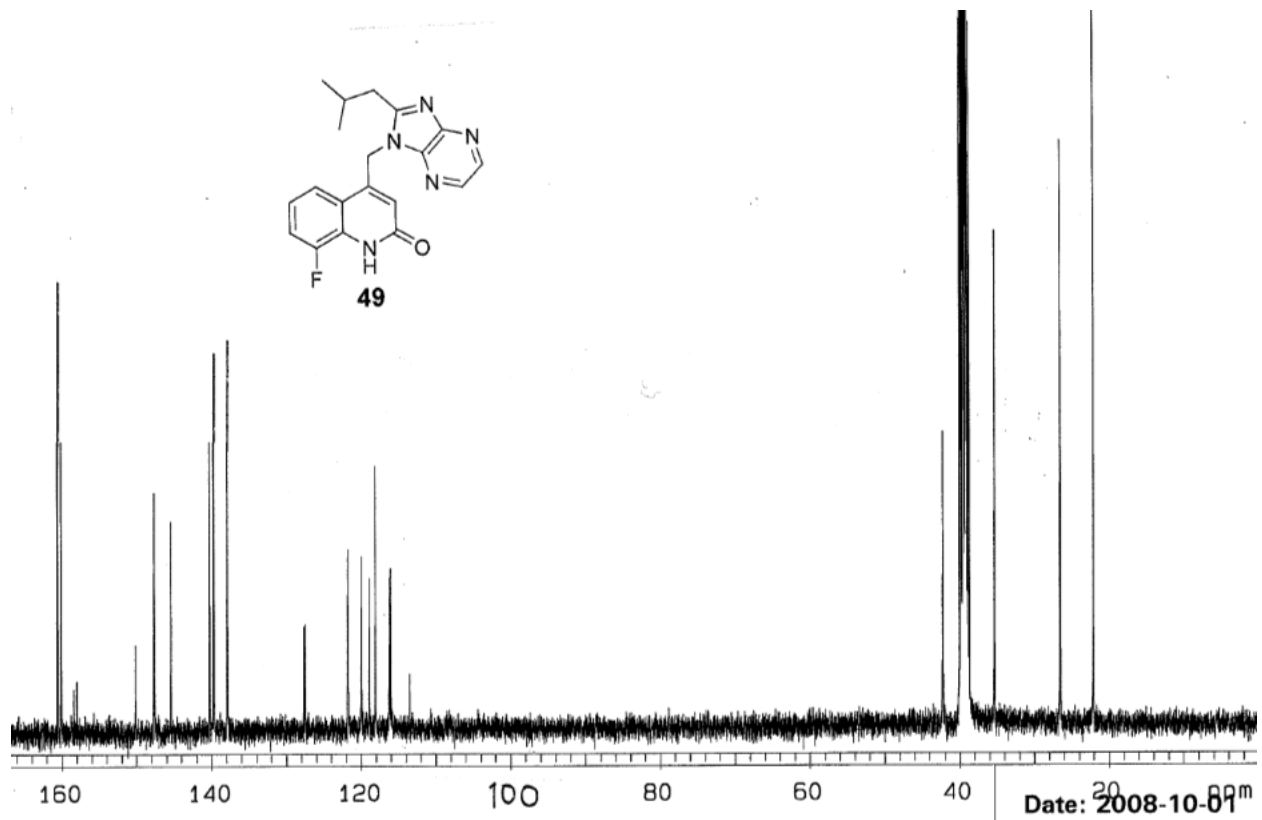
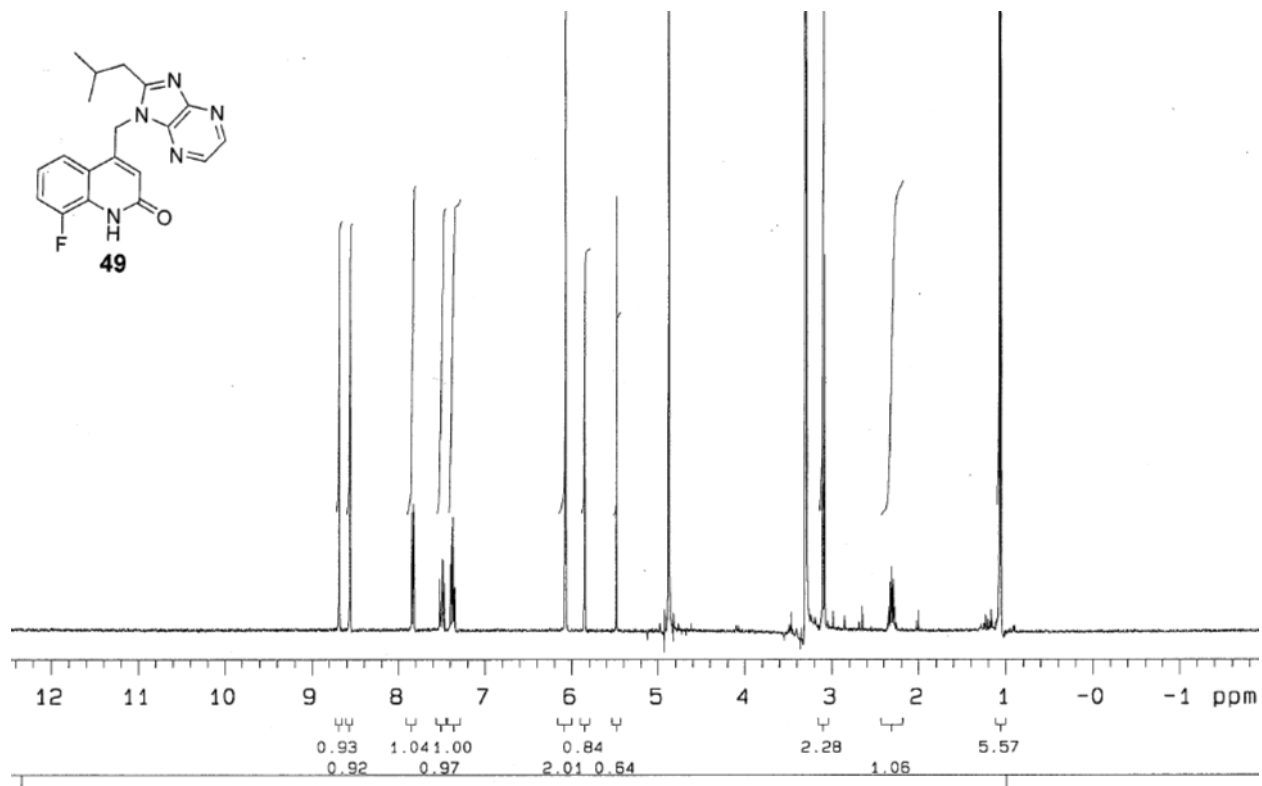
Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.350	BB	0.0472	7.82130	2.21291	0.2303
2	4.174	BV	0.1919	50.75851	3.84794	1.4944
3	4.690	VB	0.2489	3338.10938	208.40991	98.2754

```
Totals :                      3396.68918  214.47077
```

Compound 48: 4-((2-Cyclobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-8-fluoroquinolin-2(1H)-one

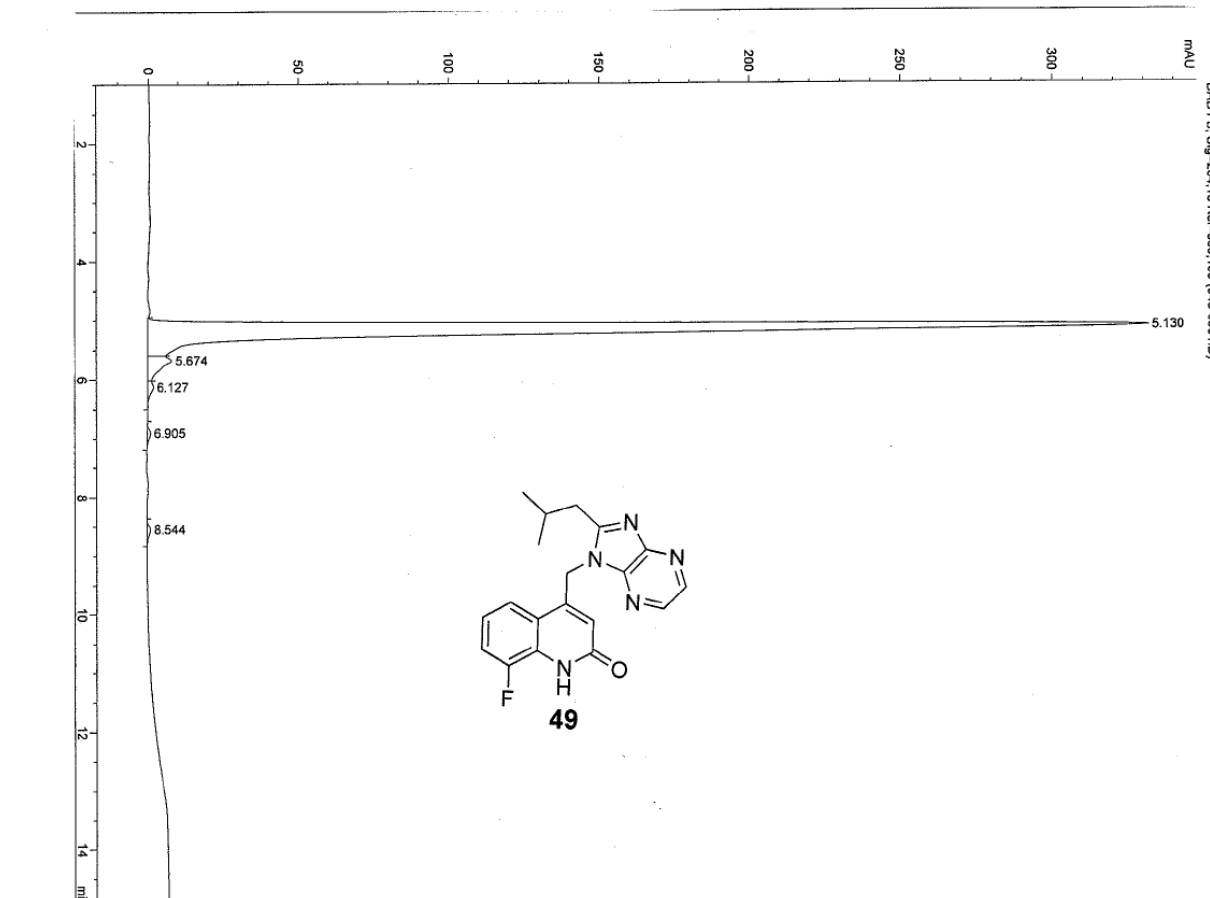




```

=====
Injection Date : 11/3/2008 12:38:08 PM      Seq. Line : 9
Sample Name    :                               Location  : Vial 43
Acq. Operator  : 1                             Inj       : 1
Acq. Instrument : Kalypsys                       Inj Volume: 5 µl
Sequence File  : C:\CHEM32\1\SEQUENCE\DEF_LC2.S
Method        : C:\CHEM32\1\METHODS\1-95_LC.M
Last changed   : 11/3/2008 10:20:09 AM by 1
1%-95% AcCN in H2O, .05%TFA
=====

```



=====
Area Percent Report
=====

```

Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

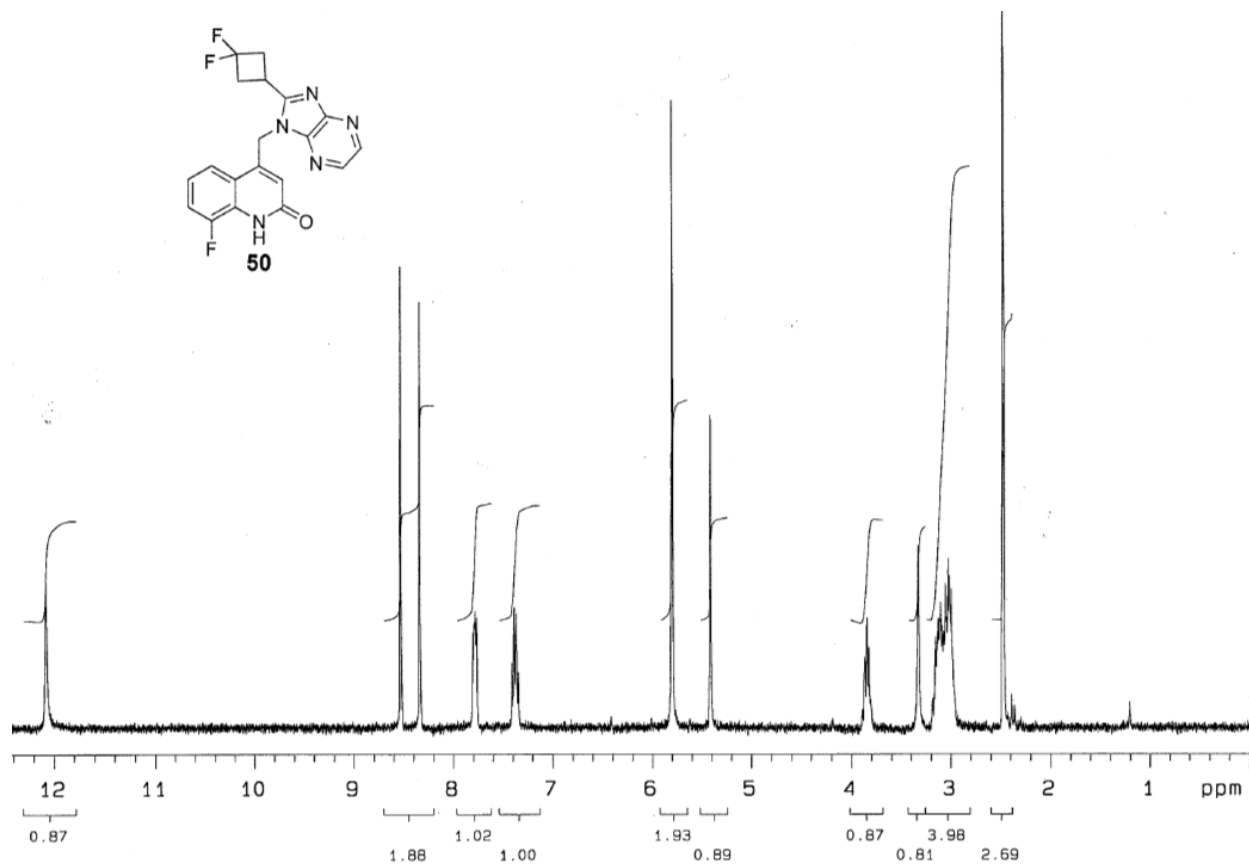
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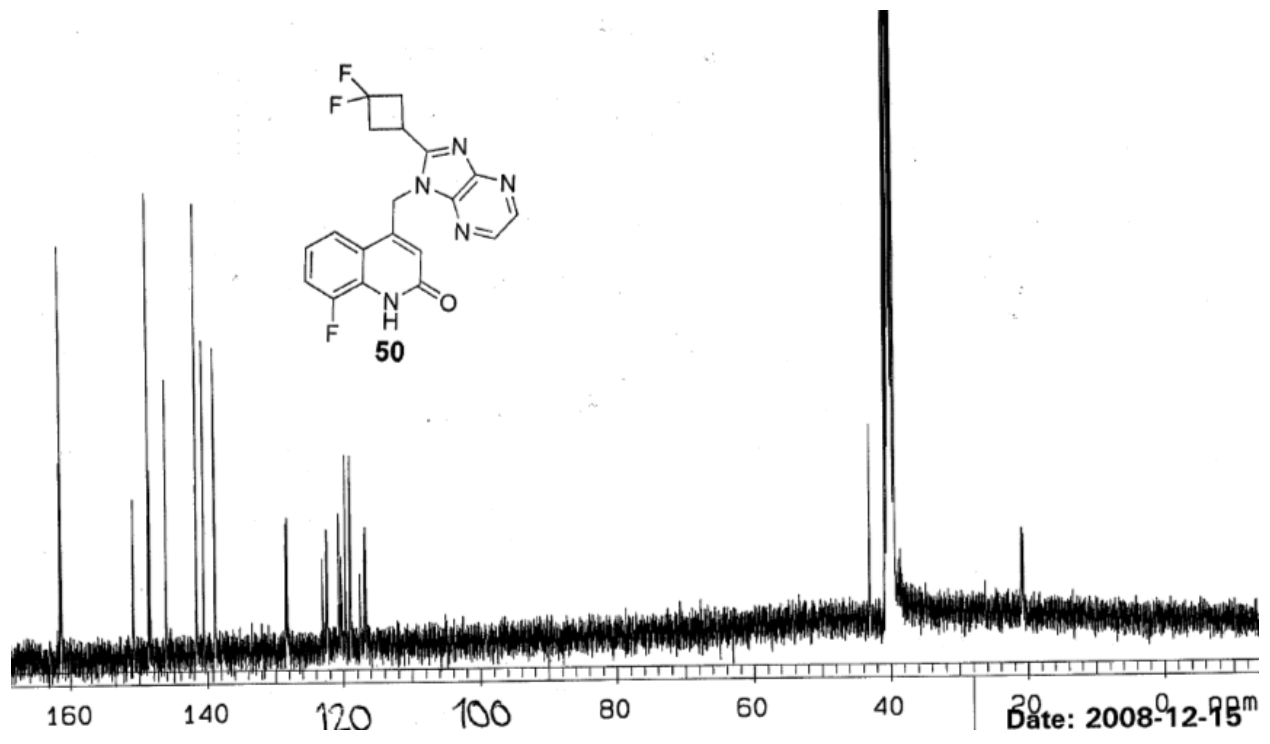
Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.130	VV	0.1710	3669.67505	331.86118	95.5675
2	5.674	VV	0.1965	118.96457	8.23702	3.0981
3	6.127	VB	0.1758	25.71061	2.00257	0.6696
4	6.905	BB	0.1591	11.98578	1.13588	0.3121
5	8.544	BB	0.1692	13.54214	1.16827	0.3527

Totals : 3839.87815 344.40492

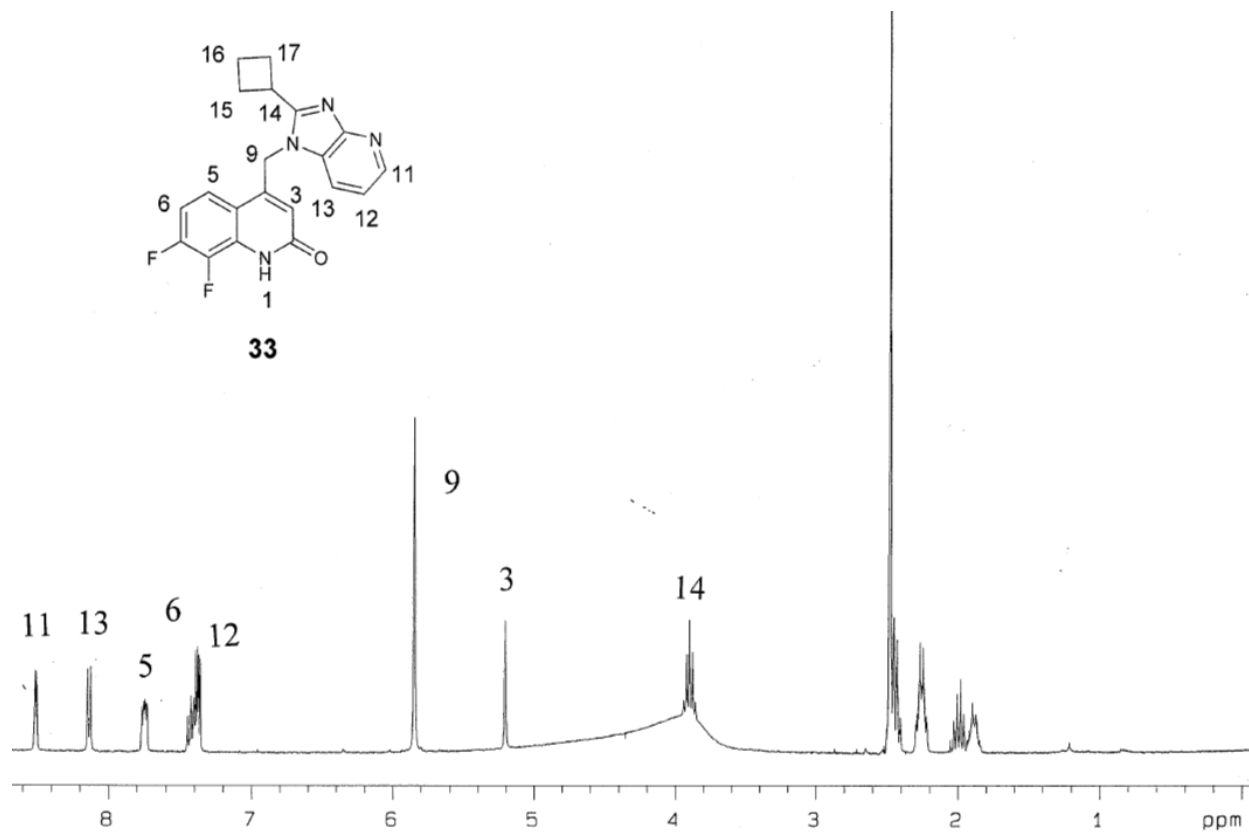
Compound 50: 4-((2-(3,3-Difluorocyclobutyl)-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-8-fluoroquinolin-2(1H)-one

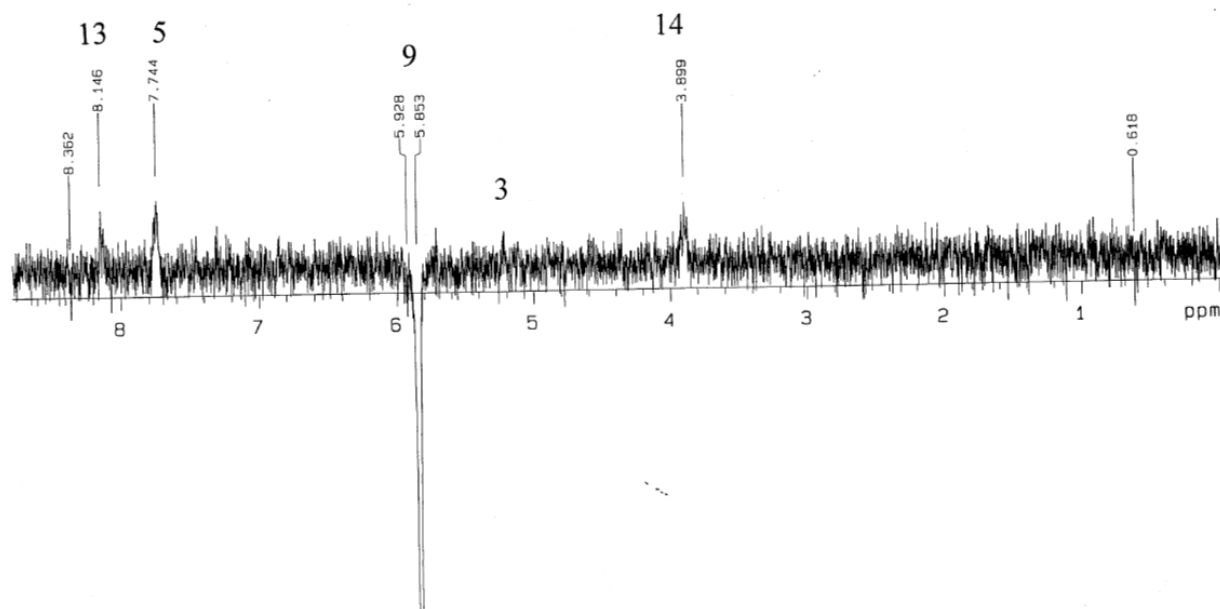




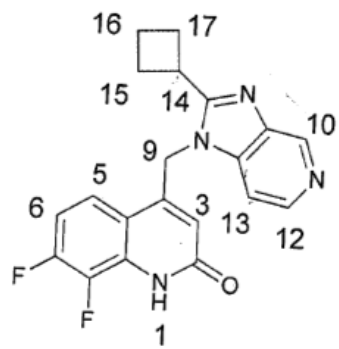
NOE Experiments

NOE Experiments for Compound 33 (Irradiation of proton #9)

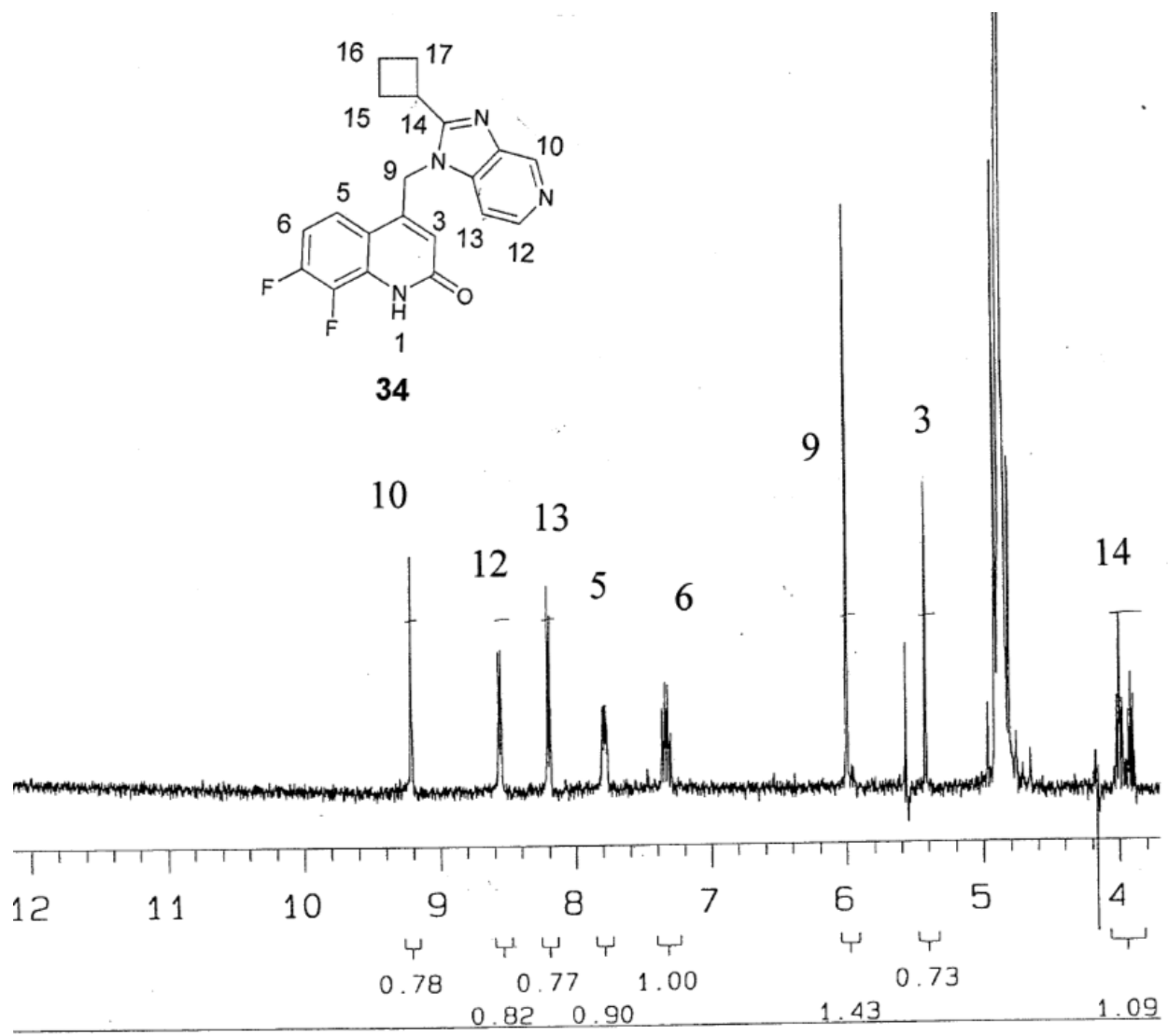


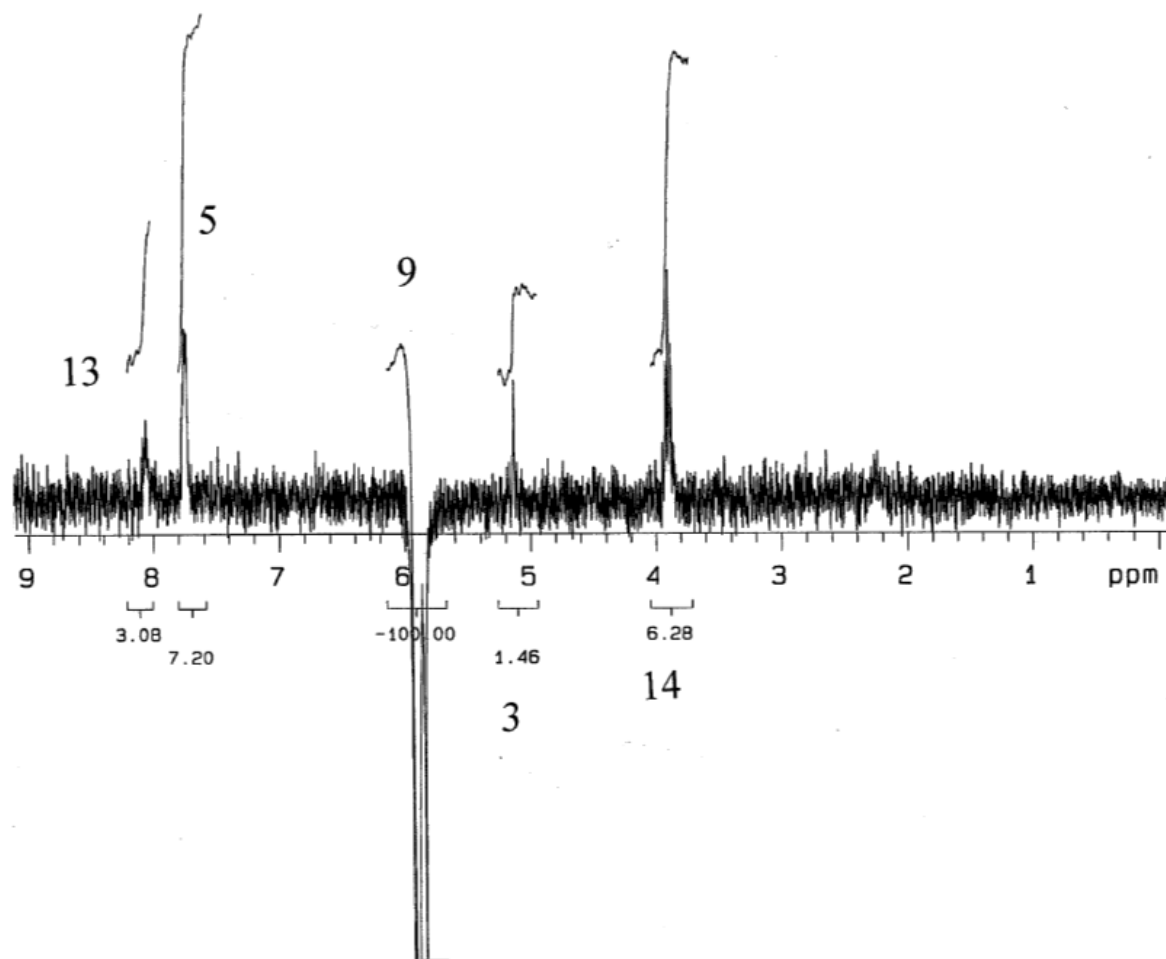


NOE Experiments for Compound 34 (Irradiation of proton #9)



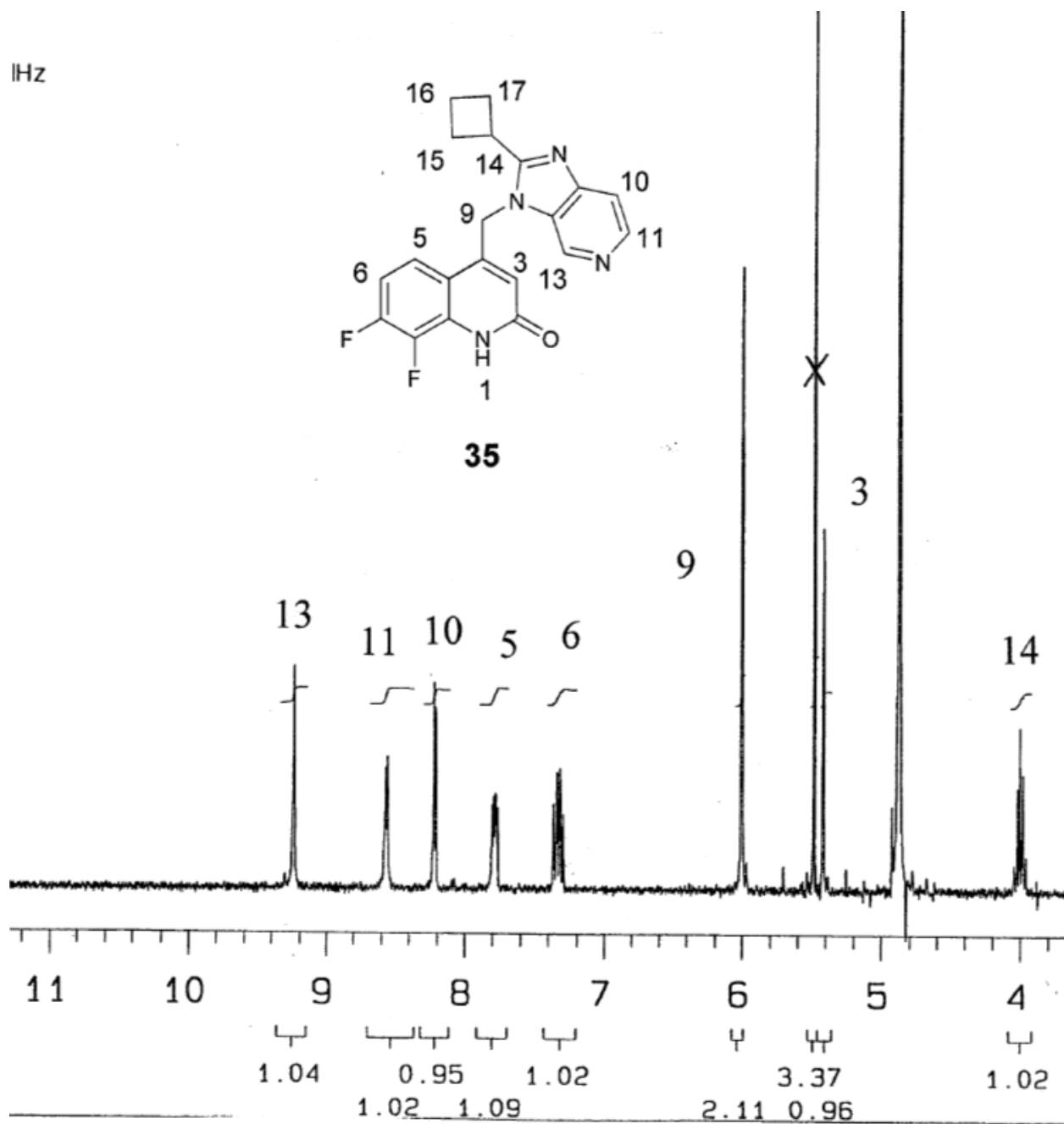
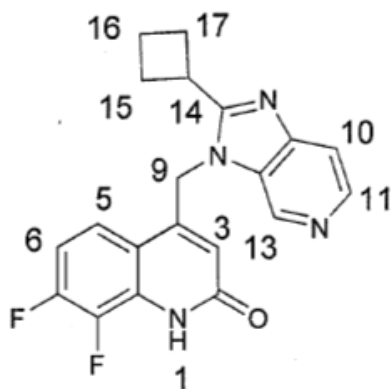
34

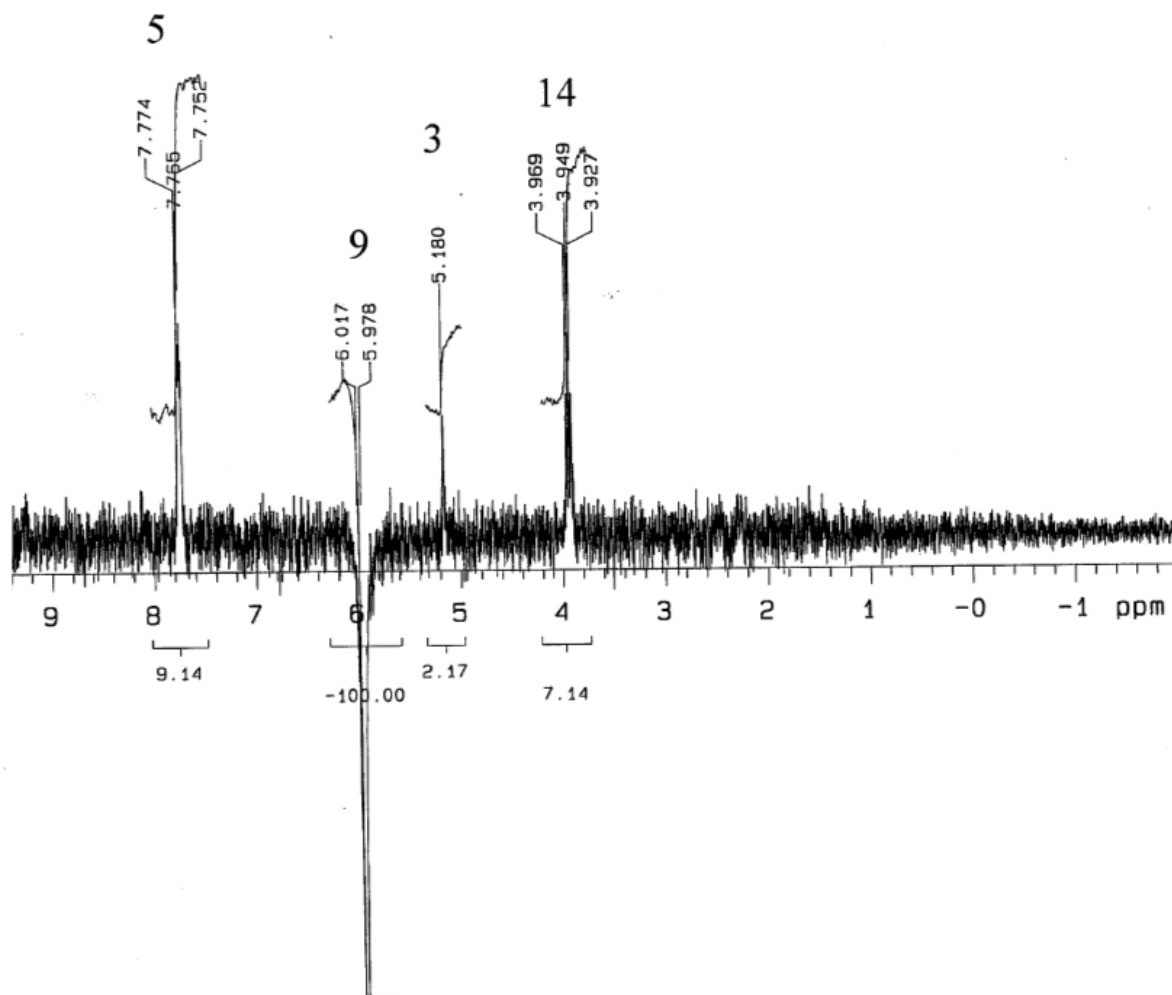




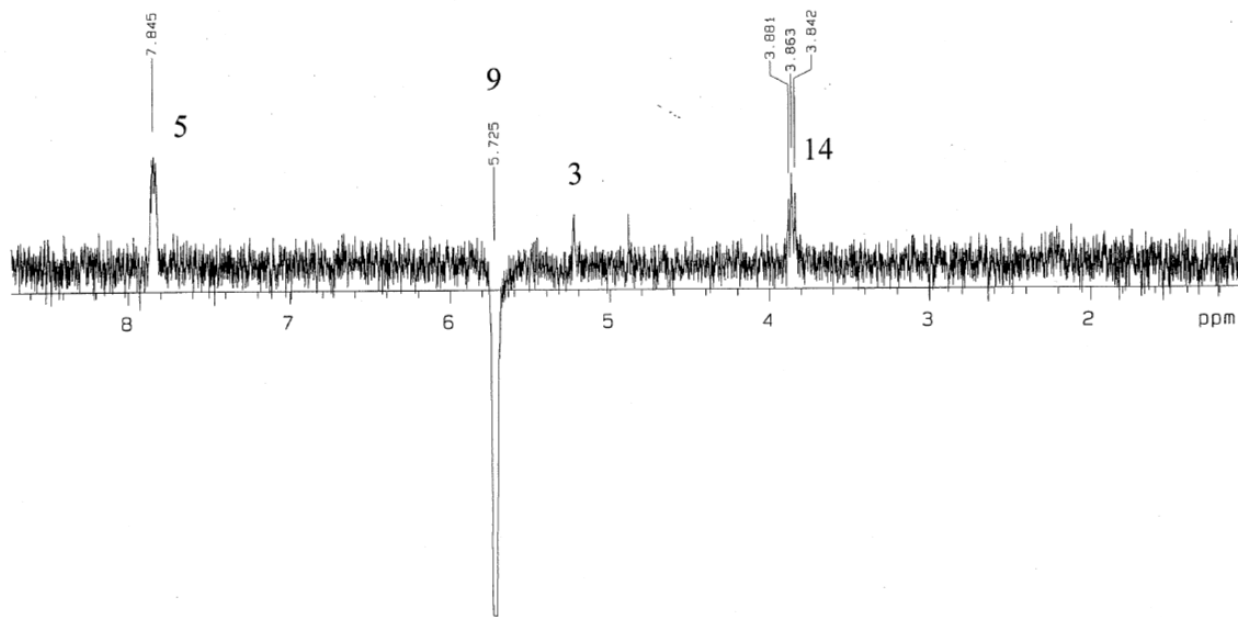
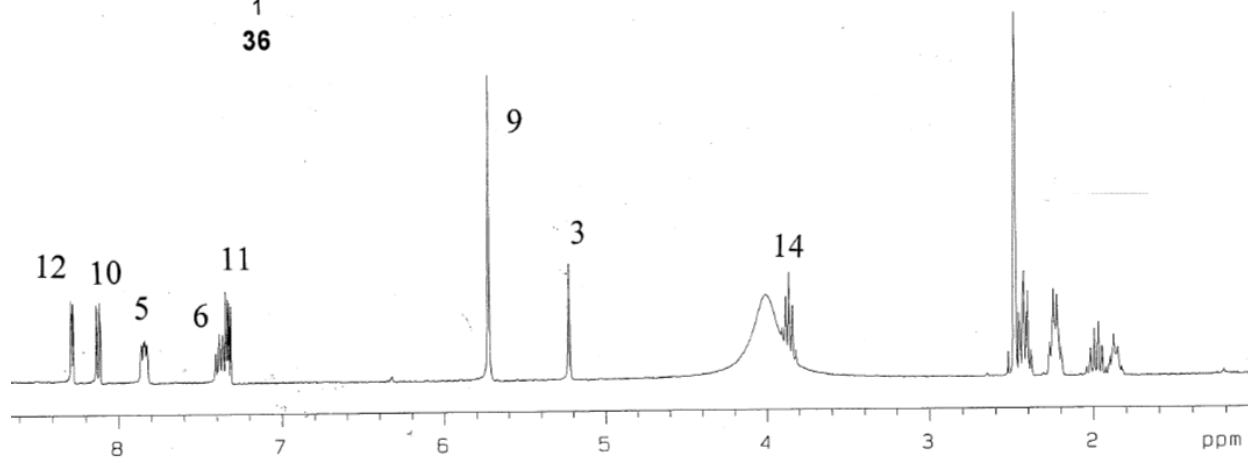
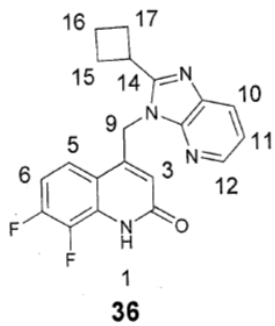
NOE Experiments for Compound 35 (Irradiation of proton #9)

1H NMR





NOE Experiments for Compound 36 (Irradiation of proton #9)



High Resolution Mass Spectrum (table format).

Compound	MF	MW	ESI+ Exact m/z	ESI+ Measured m/z	ESI+ Mass Defect (ppm)	ESI- Exact m/z	ESI- Measured m/z	ESI- Mass Defect (ppm)
10	C21H15N4OFS	390.0951	391.1029			389.0873	389.0872	-0.26
12	C21H14N4OF2S	408.0856	409.0934			407.0778	407.0779	0.25
13	C20H12N4OF2S	394.0700	395.0778			393.0622	393.0619	-0.76
14	C21H15N5OF2	391.1245	392.1323			390.1167	390.1167	0.00
15	C23H16N4OF2	402.1292	403.1370			401.1214	401.1211	-0.75
16	C22H14N4OF2	388.1136	389.1214			387.1058	387.1058	0.00
17	C22H14N4OF2	388.1136	389.1214			387.1058	387.1059	0.26
18	C22H14N4OF2	388.1136	389.1214			387.1058	387.1056	-0.52
19	C23H16N4OF2	402.1292	403.1370			401.1214	401.1216	0.50
20	C20H17N3OF2	353.1340	354.1418			352.1262	352.1259	-0.85
21	C19H15N3OF2	339.1183	340.1261			338.1105	338.1109	1.18
22	C21H19N3OF2	367.1496	368.1574			366.1418	366.1418	0.00
23	C20H17N3OF2	353.1340	354.1418			352.1262	352.1259	-0.85
24	C20H15N3OF2	351.1183	352.1261			350.1105	350.1102	-0.86
25	C21H17N3OF2	365.1340	366.1418			364.1262	364.1258	-1.10
26	C22H19N3OF2	379.1496	380.1574			378.1418	378.1416	-0.53
27	C23H21N3OF2	393.1653	394.1731			392.1575	392.1573	-0.51
28	C21H19N3OF2	367.1496	368.1574			366.1418	366.1415	-0.82
29	C22H21N3OF2	381.1653	382.1731			380.1575	380.1569	-1.58
30	C21H17N3OF2	365.1340	366.1418			364.1262	364.1258	-1.10
31	C22H19N3OF2	379.1496	380.1574	380.1571	-0.79	378.1418	378.1413	-1.32
32	C23H21N3OF2	393.1653	394.1731			392.1575	392.1573	-0.51
33	C20H16N4OF2	366.1292	367.1370			365.1214	365.1215	0.27
34	C20H16N4OF2	366.1292	367.1370			365.1214	365.1209	-1.37
35	C20H16N4OF2	366.1292	367.1370			365.1214	365.1214	0.00
36	C20H16N4OF2	366.1292	367.1370			365.1214	365.1211	-0.82

37	C21H18N4OF2	380.1449	381.1527			379.1371	379.1369	-0.53
38	C20H15N4OF2Cl	400.0902	401.0980			399.0824	399.0819	-1.25
39	C21H18N4O2F2	396.1398	397.1476	397.1475	-0.25	395.1320		
40	C22H21N5OF2	409.1714	410.1792			408.1636	408.1638	0.49
41	C21H15N4OF5	434.1166	435.1244			433.1088	433.1090	0.46
42	C19H15N5OF2	367.1245	368.1323	368.1318	-1.36	366.1167	366.1170	0.82
44	C20H17N5OF2	381.1401	382.1479			380.1323	380.1326	0.79
45	C19H17N5OF2	369.1401	370.1479	370.1478	-0.27	368.1323	368.1318	-1.36
46	C18H15N5OF2	355.1245	356.1323			354.1167	354.1161	-1.69
47	C19H13N5OF4	403.1056	404.1134	404.1130	-0.99	402.0978	402.0983	1.24
48	C19H16N5OF	349.1339	350.1417			348.1261	348.1258	-0.86
49	C19H18N5OF	351.1495	352.1573			350.1417	350.1415	-0.57
50	C19H14N5OF3	385.1150	386.1228	386.1229	0.26	384.1072	384.1074	0.52