Supporting Information:

Quinoxalinone Inhibitors of the Lectin DC-SIGN

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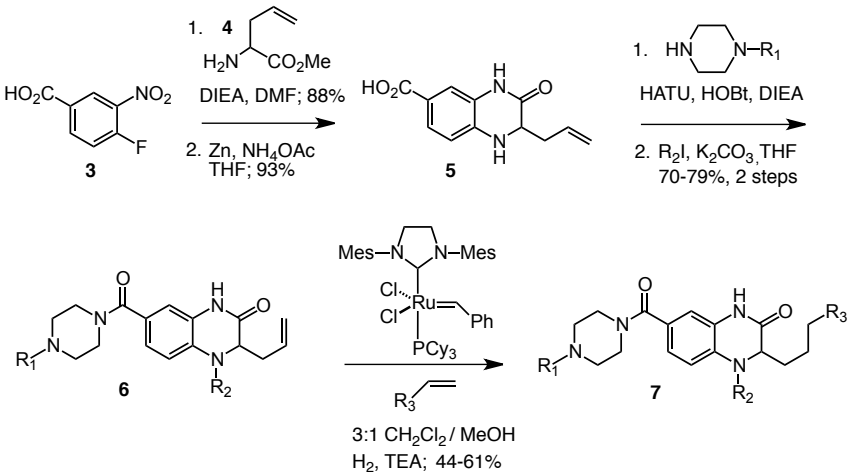
General Procedures and Materials. All moisture- and oxygen-sensitive reactions were carried out in flame-dried glassware under a nitrogen or argon atmosphere. Unless otherwise noted, all reagents and solvents were the highest commercially available grades and used without further purification. Grubbs 2nd generation catalyst ([1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene) (tricyclohexylphosphine)ruthenium), 4-vinylbenzoic, 2-methyl styrene, 1-(2-methoxyphenyl)piperazine, 1-(4-(pyridylpiperazine)), and 1-(2-(pyrimidylpiperazine), HOBt (1-hydroxybenzotriazole) and HATU (7-azabenzotriazolyl-N,N,N',N'-tetramethyluronium hexafluorophosphate were was purchased from Sigma-Aldrich. Dichloromethane (CH_2Cl_2) and diisopropylethylamine (DIEA) were distilled from calcium hydride, methanol (MeOH) was distilled from magnesium, and water (H_2O) was purified with a MilliQ purification system (Millipore). Analytical thin layer chromatography (TLC) was used to monitor reactions and was performed on 0.25 mm pre-coated Silica Gel 60 F254 (Merck). Compounds were visualized with ultraviolet light (254 nm) and/or charring with ninhydrin stain (0.3 g ninhydrin, 100 mL *n*-butanol, 2 mL AcOH), ceric ammonium molybdate stain (10 g ammonium molybdate, 4 g ceric ammonium sulfate, 40 mL H_2SO_4, 360 mL H_2O), or potassium permanganate stain (1.5 g $KMnO_4$, 10 g K_2CO_3, 2.5 mL 5% aqueous NaOH, 150 mL H_2O). Flash chromatography

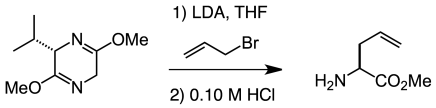
was performed on Scientific Adsorbents silica gel (32-63 m; 60 Å pore size).

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AC-300 or Varian Inova-500 spectrometers, and chemical shifts are reported relative to tetramethylsilane or residual solvent peaks in parts per million ($CHCl_3$: ^{1}H: δ 7.26, ^{13}C: δ 77.0; DMSO: ^{1}H: δ 2.50, ^{13}C: δ 39.5; CH_3OH: ^{1}H: δ 3.31, ^{13}C: δ 49.0) Peak multiplicity is reported as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), etc. High resolution electrospray ionization mass spectra (HRESI-MS) were obtained on a Micromass LCT (electrospray ionization, time-of-flight analyzer).

S1. Synthetic Procedures



Methyl 2-amino-4-pentenoate (4)

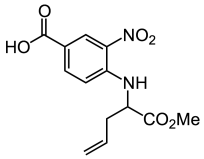


A solution of lithium diisopropylamine (88 mL, 0.50 M in THF, 44 mmol) was added to a stirred solution of the bislactim ether (7.36 g, 40.0 mmol) in anhydrous THF (120 mL) at -78 ^{o}C. The reaction mixture was stirred for 20 min. A solution of allyl bromide (5.32 g, 44.0 mmol) in THF (80 mL) was added dropwise over the course of 15 min. The reaction mixture was stirred for 12 h and quenched with water (80 mL). The crude reaction mixture was warmed to room temperature and the solvent removed in vacuo. The residue was diluted with water (80 mL) and extracted with EtOAc (2 x 200 mL) and brine (1 x 200 mL). The organic layer was dried over $MgSO_4$ and concentrated.

The allyl bislactim ether was dissolved in THF (200 mL). A solution of 0.10 M HCl (68 mL) was added and the reaction mixture stirred at room temperature for 12 h. The pH was adjusted to 11 with concentrated NH_4OH (28-30%) and the resulting mixture was subjected to extraction with EtOAc (2 x 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (4:1 CH_2Cl_2:MeOH) to give 4.60 g (81%) of **4** as a white solid. $[\alpha]^{22} = +3.1$ (c 0.85 MeOH).

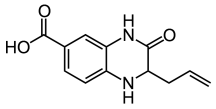
^{1}H NMR (300 MHz, d_6-DMSO) δ 8.90 (bs, 2H), 5.83-5.69 (m, 1H), 5.16-5.07 (m, 2H), 4.02 (t, J = 6.1 Hz, 1H), 3.67 (s, 3H), 2.59 (dd, J = 7.0, 6.3 Hz, 2H). ^{13}C NMR (75 MHz, d_6-DMSO) δ 169.84, 132.04, 120.41, 53.26, 52.25. 34.75.
HRMS (EMM) calcd for $C_6H_{11}NO_2$ $[M+H]^+$: 130.0863, found 130.0860.

4-((1-methoxy-1-oxopent-4-en-2-yl)amino)-3-nitrobenzoic acid



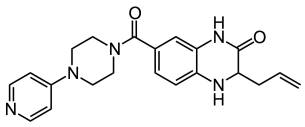
4-Fluoro-3-nitrobenzoic acid (4.00 g, 21.6 mmol) was dissolved in anhydrous THF (43 mL) under Ar(g). The base N,N-diisopropylethylamine (23.0 mL, 132 mmol) was added followed by aminopentenoate **4** (3.90 g, 30.2 mmol). The resulting solution was heated to 70 ^{o}C and allowed to stir for 12 h. The solvent was removed under reduced pressure and the crude residue dissolved in EtOAc (100 mL). The organic layer was extracted with 1 M HCl (3 x 100 mL) and brine (1 x 100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by column chromatography (19:1 CH_2Cl_2:MeOH) to give 5.6 g (88%) of **5** as a yellow solid.
^{1}H NMR (300 MHz, CD_3OD) δ 8.81 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 8.9, 2.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 5.84-5.75 (m, 1H), 5.26-5.18 (m, 2H), 4.66 (t, J = 5.7 Hz, 1H), 3.78 (s, 3H), 2.75 (dd, J = 7.2, 6.1 Hz, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 171.88, 166.98, 146.41, 136.30 (2C), 131.96, 128.95, 119.20, 118.61, 114.31, 54.92, 51.96, 36.13
HRMS (EMM) calcd for $C_{13}H_{14}N_2O_6$ $[M+H]^+$: 295.0925, found 295.0917.

2-allyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (5)



The nitrobenzoic acid intermediate **5** (3.00 g, 10.2 mmol) was dissolved in anhydrous THF (200 mL). To the stirring solution was added zinc metal (4.00 g, 61.2 mmol), followed by ammonium acetate (7.86 g, 102 mmol). The solution was stirred vigorously at rt for 4 h. The solution was filtered over celite and the filtrate concentrated to dryness. The crude residue was dissolved in EtOAc (100 mL) and extracted with H_2O (3 x 100 mL) and brine (1 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The product was purified by column chromatography (9:1 CH_2Cl_2:MeOH) to afford 2.2 g (93%) of **6** as a tan solid.
^{1}H NMR(300 MHz, d_6-DMSO) δ 12.22 (bs, 1H), 10.39 (s, 1H), 7.35 (dd, J = 8.2, 1.8 Hz, 1H), 7.29 (d, J = 1.6 Hz, 1H), 6.99 (s, 1H), 6.67 (d, J = 8.3 Hz, 1H), 5.85-5.71 (m, 1H), 5.10-5.01 (m, 2H), 3.97 (td, J = 5.5, 1.5 Hz, 1H), 3.38 (bs, 1H), 2.40 (dd, J = 6.7, 5.5 Hz, 2H. ^{13}C NMR (75 MHz, d_6-DMSO) δ 168.814, 166.79, 138.82, 134.32, 125.93, 125.22, 119.72, 119.01, 116.40, 112.70, 55.47, 37.75.
HRMS (EMM) calcd for $C_{12}H_{12}N_2O_3$ $(M-H)^-$: 231.0775, found 231.0775.

3-allyl-7-(4-pyridin-4-yl)piperazine-1-carbonyl)-3,4 dihydroquinoxalinone (6c)



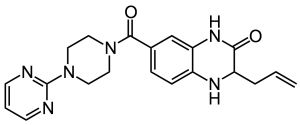
The tetrahydroquinoxaline **6** (0.50 g, 2.2 mmol) was dissolved in anhydrous DMF (4.3 mL) under Ar(g). The base N,N-

diisopropylethylamine (1.1 mL, 6.3 mmol) was added followed by HATU (0.90 g, 2.4 mmol) and HOBt (0.32 g, 2.4 mmol). The resulting solution was allowed to stir at rt for 15 min. 1-(4-Pyridyl)piperazine (0.46 g, 2.8 mmol) was added and the reaction allowed to stir at rt for 8 h. The solvent was removed under reduced pressure and the crude residue dissolved in EtOAc (20 mL). This mixture was extracted with 1 M HCl (3 x 20 mL), saturated $NaHCO_3$ (3 x 20 mL) and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by column chromatography (10:1 to 4:1 CH_2Cl_2:MeOH) to afford 0.66 g (81%) of compound 7c as a clear oil.

^{1}H NMR (300 MHz, CD_3OD) δ 8.14 (d, J = 4.6 Hz, 2H), 7.01 (dd, J = 8.0, 1.8 Hz, 1H), 6.92 (d, J = 1.9 Hz, 1H), 6.86 (d, J = 6.6 Hz, 2H), 6.75 (d, J = 8.1 Hz, 1H), 5.91-5.77 (m, 1H), 5.14-5.09 (m, 2H), 3.98 (dd, J = 7.0, 5.2 Hz, 1H), 3.98 (bs, 4H), 3.49 (bs, 4H), 2.54-2.42 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 171.69, 168.35, 155.60, 148.54(2C), 136.37, 133.24, 125.05, 123.87, 123.74, 118.07, 114.66, 112.88, 108.47(2C), 55.71, 45.59(4C), 37.22.

HRMS (EMM): calcd for $C_{21}H_{23}N_5O_2$ $(M+H)^+$ 378.1925: found, 378.1931.

3-allyl-7-(4-pyrimidin-2-yl)piperazine-1-carbonyl)-3,4-dihydroquinoxalin-2-(1H)-one (6b)

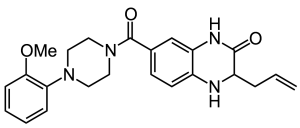


The tetrahydroquinoxaline **6** (0.50 g, 2.2 mmol) was dissolved in anhydrous DMF (4.3 mL) under Ar(g). The base N,N-diisopropylethylamine (1.1 mL, 6.3 mmol) was added followed by HATU (0.90 g, 2.4 mmol) and HOBt (0.32 g, 2.4 mmol). The resulting solution was allowed to stir at rt for 15 min. 1-(2-Pyrimidyl)piperazine (0.46 g, 2.8 mmol) was added and the reaction allowed to stir at rt for 8 h. The solvent was removed under reduced pressure and the crude residue dissolved in EtOAc (20 mL). This was extracted with 1 M HCl (3 x 20 mL), saturated $NaHCO_3$ (3 x 20 mL) and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by column chromatography (10:1 to 5:1 EtOAc:MeOH) to afford 0.68 g (84%) of a light yellow solid.

^{1}H NMR(300 MHz, $CDCl_3$) δ 9.03 (bs, 1H), 8.28 (d, J = 4.8 Hz, 2H), 6.96 (d, J = 1.7 Hz, 1H), 6.92 (dd, J = 8.0, 1.6 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.47 (t, J = 4.8 Hz, 1H), 5.80-5.66 (m, 1H), 5.18-5.08 (m, 2H), 4.25 (bs, 1H), 3.87 (dd, J = 6.4, 3.4 Hz, 1H), 3.80 (bs, 4H), 3.65 (bs, 4H), 2.72-2.64 (m, 1H), 2.39-2.28 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.64, 167.84, 161.77, 158.00, 134.80, 133.42, 126.17, 125.48, 123.62, 120.06, 115.65, 115.58, 113.44, 110.69, 55.07, 44.05(4C), 36.68.

HRMS (EMM) calcd for $C_{20}H_{22}N_6O_2$ $[M+Na]^+$ 401.1697: found, 401.1694.

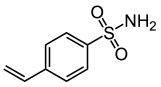
3-allyl-7-(4-(2-methoxyphenyl)piperazine-1-carbonyl)-3,4-dihydroquinoxalin-2-(1H)-one (6a)



The tetrahydroquinoxaline **6** (0.50 g, 2.2 mmol) was dissolved in anhydrous DMF (4.3 mL) under Ar(g). The base N,N-

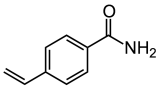
diisopropylethylamine (1.1 mL, 6.3 mmol) was added followed by HATU (0.90 g, 2.4 mmol) and HOBt (0.32 g, 2.4 mmol). The resulting solution was allowed to stir at rt for 15 min. 1-(2-Methoxyphenyl)piperazine (0.46 g, 2.8 mmol) was added and the reaction allowed to stir at rt for 8 h. The solvent was removed under reduced pressure and the crude residue dissolved in EtOAc (20 mL). This was extracted with 1 M HCl (3 x 20 mL), saturated $NaHCO_3$ (3 x 20 mL) and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by column chromatography (20:1 to 10:1 CH_2Cl_2:MeOH) to afford 0.77 g (88%) of a light yellow oil.
^{1}H NMR(300 MHz, CD_3OD) δ 7.05-6.87 (m, 6H), 6.75 (d, J = 7.9 Hz), 5.91-5.77 (m, 1H), 5.14-5.08 (m, 2H), 3.96 (dd, J = 7.2, 5.2 Hz, 1H), 3.85 (s, 3H), 3.77 (bs, 4H), 3.03 (bs, 4H), 2.50-2.42 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 171.52, 168.42, 152.76, 140.79, 136.15, 133.26, 125.02, 124.28, 123.75, 123.65, 121.02, 118.61, 118.03, 114.59, 112.93, 111.68, 55.72, 54.80, 50.98(4C), 37.17.
HRMS (EMM): calcd for $C_{23}H_{26}N_4O_3$ $[M+H]^+$ 407.2078; found, 407.2073.

4-vinylbenzenesulfonamide



4-Vinylbenzenesulfonate (10.0 g, 48.5 mmol) was added portionwise to a stirring solution of thionyl chloride (28.5 mL, 393 mmol) at rt. To this mixture was added DMF (4.1 mL) and the reaction was stirred for 4 h. Diethyl ether (150 mL) was added and the mixture cooled to 0 °C. Ice water (150 mL) was added gradually and the organic layer was removed. The ether layer was added immediately to a stirring solution of concentrated NH_4OH (28-30%) (145 mL) at rt. The reaction mixture was stirred for 3 h and at this time, TLC indicated no starting material. The reaction mixture was neutralized by adding 1 M HCl until a pH of 7 was reached. The organic layer was extracted, washed with brine (1 x 250 mL) and dried over anhydrous Na_2SO_4. This was filtered and concentrated to dryness. The product was purified by flash chromatography (EtOAc) to afford 6.0 g (70%) of a white solid.
^{1}H NMR (300 MHz, d_6-DMSO) δ 7.77 (dd, J = 8.4, 1.6 Hz, 2H), 7.64 (dd, J = 8.4, 1.5 Hz, 2H), 7.33 (bs, 2H), 6.79 (dd, J = 17.6, 10.9 Hz, 1H), 5.97 (d, J = 17.7 Hz, 1H), 5.40 (d, J = 10.9 Hz, 1H). ^{13}C NMR (75 MHz, d_6-DMSO) δ 143.87, 141.01, 136.11, 127.16(2C), 126.69(2C), 117.87.
HRMS (EMM): calcd for $C_8H_9NO_2S$ $[M+Na]^+$: 206.0247, found 206.0256.

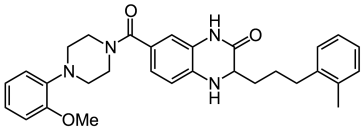
4-vinylbenzamide



4-Vinylbenzoic acid (3.0 g, 20.3 mmol) was dissolved in CH_2Cl_2 (50 mL) under N_2(g). To this mixture was added N-hydroxysuccinimide (3.30 g, 28.3 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (5.4 g, 28.3 mmol). The reaction was stirred at rt for 8 h. The solvent was removed in vacuo and the crude residue dissolved in EtOAc (50 mL) and extracted with 1 M HCl (3 x 50 mL), saturated $NaHCO_3$ (3 x 50 mL), and brine (1 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The product was purified by flash chromatography (EtOAc) to afford 4.3 g (86%) of a white solid.

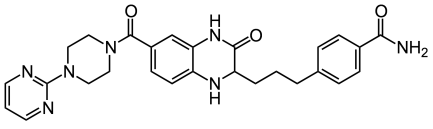
The solid was dissolved in acetonitrile (180 mL) and added to a stirring solution of concentrated NH_4OH (28-30%) (180 mL). The resulting mixture was stirred at rt for 3 h. The acetonitrile was removed in vacuo and the crude residue dissolved in EtOAc (150 mL). The organic layer was removed and the aqueous layer was neutralized with 1M HCl and extracted with EtOAc (3 x 150 mL). The organic layers were combined and washed with brine (1 x 150 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude residue purified by flash chromatography (EtOAc) to afford 1.83 g (71%) as a white solid.
^{1}H NMR (300 MHz, d_6-DMSO) δ 7.98 (bs, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 7.37 (bs, 1H), 6.75 (dd, J = 17.9, 11.0 Hz, 1H), 5.91 (dd, J = 17.9, 0.80 Hz, 1H), 5.32 (dd, J = 11.0, 0.80 Hz, 1H). ^{13}C NMR (75 MHz, d_6-DMSO) δ 168.28, 140.48, 136.61, 134.15, 128.55(2C), 126.59(2C), 116.77.
HRMS (EMM): calcd for C_9H_9NO $[M+Na]^+$: 170.0577, found 170.0580.

7-(4-(2-methoxyphenyl)piperazine-1-carbonyl)-3-(o-tolyl)propyl)-3,4-dihydroquinoxalin-2-one (20)



2-Methylstyrene (0.12 g, 1.0 mmol) was dissolved in CH_2Cl_2 (0.50 mL) under Ar(g) at rt. To this was added Grubbs 2nd generation catalyst (21.2 mg, 0.025 mmol) as a solution in CH_2Cl_2 (0.20 mL) at rt. The reaction was stirred at rt for 20 min and then heated to 50 ^{o}C. Compound **7a** (0.10 g, 0.25 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2:CH_3OH (1.0 mL) and added dropwise to the refluxing solution. The reaction was stirred until TLC indicated conversion of compound **7a**. The reaction was purged with hydrogen (1 atm) and allowed to stir under an atmosphere of H_2 for 9 h. The solvent was removed in vacuo and the crude residue purified by column chromatography (15:1 to 1:15 hexanes:EtOAc) to afford 86.0 mg (69%) of **9** as a tan oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (bs, 1H), 7.07-6.80 (m, 11H), 6.53 (d, J = 8.5 Hz, 1H), 4.02 (bs, 1H), 3.90 (t, J = 7.1 Hz, 1H), 3.80 (s, 3H), 3.76 (bs, 4H), 2.95 (bs, 4H), 2.57 (t, J = 7.6 Hz, 2H), 2.21 (s, 3H), 1.84-1.62 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.29, 168.04, 152.49, 140.90, 140.09, 136.05, 134.78, 130.48, 128.96, 126.33, 126.21, 126.15, 125.28, 123.77, 123.59, 121.29, 118.69, 115.55, 113.14, 111.55, 101.28, 56.43, 55.65, 51.18(4C), 33.09, 32.55, 25.99, 19.56.
HRMS (EMM) calcd for $C_{30}H_{34}N_4O_3$ $[M+Na]^+$: 521.2524, found 521.2537.

N-(4-(3-(3-oxo-6-(4-(pyrimidin-2-yl)piperazine-1-carbonyl)-1,2,3,4-tetrahydroquinoxalin-2-yl)propyl)phenyl)acetamide (21)



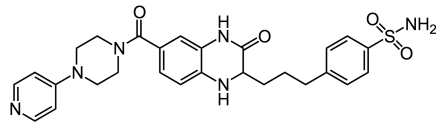
4-Vinylbenzamide (0.147 g, 1.0 mmol) was dissolved in a 4:1 mixture of CH_2Cl_2:MeOH (0.50 mL) under Ar(g) at rt. To this was added Grubbs 2nd generation catalyst (21.2 mg, 0.025 mmol) as a solution in CH_2Cl_2 (0.20 mL) at rt. The reaction was stirred at rt for 20 min and then heated to 50 ^{o}C. Compound **7b** (0.10 g, 0.25 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2:MeOH (1.0 mL) and added dropwise to the

refluxing solution. The mixture was stirred until TLC indicated conversion of compound **7b**. The reaction was purged with hydrogen (1 atm) and allowed to stir under an atmosphere of H_2 for 9 h. The solvent was removed in vacuo and the resulting residue purified by column chromatography (10:1 to 1:1 CH_2Cl_2:MeOH) to afford 65.0 mg (52%) of **11** as a tan oil.

^{1}H NMR (300 MHz, CD_3OD) δ 8.25 (d, J = 4.9 Hz, 2H), 7.75 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.28 (dd, J = 8.2, 1.5 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 1.5 Hz, 1H), 6.54 (t, J = 4.9 Hz, 1H), 3.87-3.46 (m, 10H), 2.85 (t, J = 7.6 Hz, 2H), 2.74 (dt, J = 7.6, 7.2 Hz, 2H), 2.09 (p, J = 7.6 Hz, 2H). ^{13}C NMR (125 MHz, d_6-DMSO) δ 170.25, 168.48, 167.95, 161.81, 158.64 (2C), 147.88, 136.43, 132.41, 128.45(2C), 128.21(2C), 125.58, 124.39, 123.51, 115.13, 112.77, 111.13, 55.41, 44.06(4C), 34.95, 28.68, 18.44.

HRMS (EMM) calcd for $C_{27}H_{29}N_7O_3$ $[M+H]^+$: 500.2322, found 500.2331.

4-(3-(3-oxo-6-(4-(pyridin-4-yl)piperazine-1-carbonyl)-1,2,3,4-tetrahydroquinoxalin-2-yl)propyl)benzenesulfonamide (22)



4-Vinylbenzenesulfonamide (0.18 g, 1.0 mmol) was dissolved in CH_2Cl_2 (0.50 mL) under Ar(g) at rt. To this was added Grubbs 2nd generation catalyst (21.2 mg, 0.025 mmol) as a solution in CH_2Cl_2 (0.20 mL) at rt. The reaction was stirred at rt for 20 min and then heated to 50 ^{o}C. Compound **7c** (0.10 g, 0.25 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2:MeOH (1.0 mL) and this solution was added dropwise to the refluxing solution. The mixture was stirred until TLC indicated conversion of compound **7c**. The resulting mixture was purged with hydrogen (1 atm) and allowed to stir under an atmosphere of H_2 for 9 h. The solvent was removed in vacuo and the crude residue purified by column chromatography (10:1 to 1:1 CH_2Cl_2:MeOH) to afford 65.5 mg (49%) of **13** as a tan oil.

^{1}H NMR (300 MHz, CD_3OD) δ 8.19-8.16 (m, 3H), 7.82 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.38-7.36 (m, 2H), 7.18-7.16 (m, 3H), 3.87-3.46 (m, 11H), 2.85 (t, J = 7.4 Hz, 2H), 2.74 (dt, J = 7.4, 7.2 Hz, 2H), 2.09 (p, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD) δ 171.77, 169.18, 155.91, 149.17, 147.13(2C), 141.17, 136.64, 128.22(2C), 126.10(2C), 124.99, 123.80, 123.61, 114.66, 112.75, 108.35(2C), 55.76, 45.61(4C), 34.87, 28.49, 18.00.

HRMS (EMM): calcd for $C_{27}H_{30}N_6O_4S$ $[M-H]^-$: 533.1966; found 533.1949.

S2. Production of Soluble DC-SIGN/ECD

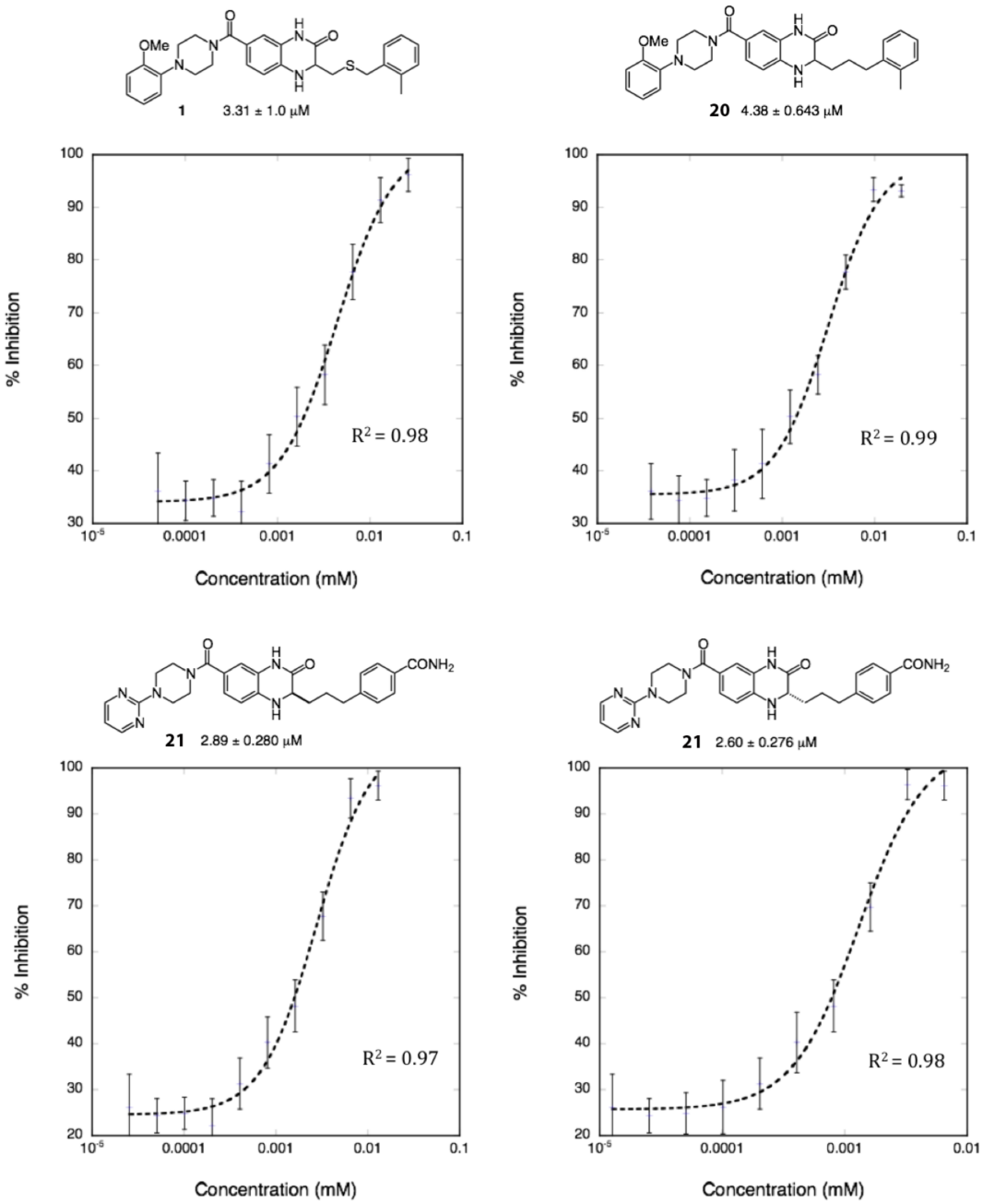
A plasmid encoding the DC-SIGN extracellular domain (ECD) was provided by Dr. Kurt Drickamer (University of Oxford).[1] The plasmid was transformed into *Escherichia coli* strain BL21/DE3 and the resulting cells were stored in 10% glycerol at -80 ^{o}C. This strain was used to inoculate a flask containing 50 mL Luria-Bertani (LB) media supplemented with ampicillin (100 μg/mL) and the culture was grown overnight at 37 ^{o}C.

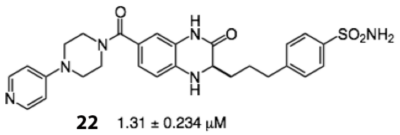
[1] Mitchell, D.A.; Fadden, A.J.; Drickamer, K.J. *J. Biol. Chem.* **2001**, 276, 28939-28945.

The culture was used to inoculate 4 L of LB (100 μg/mL ampicillin) and cells were allowed to grow at 37 ^{o}C until an OD_{600} of 0.70 was reached. Gene expression was induced with 100 mg/mL isopropyl-β-D-thiogalactoside, and the culture was incubated with shaking for 3 h at 37 ^{o}C. Bacteria were harvested by centrifugation at 8,000*g* for 10 min. Cell pellets were washed with 10 mM Tris-HCl, pH 7.8 and again centrifuged at 8,000*g* for 10 min at 4 ^{o}C. Cells were resuspended in 10 mM Tris-HCl, pH 7.8 and sonicated for 2 min. Inclusion bodies were isolated by centrifugation at 10,000*g* for 10 min at 4 ^{o}C. The pellet was solubilized in a 4 M aqueous solution of guanidine-HCl containing 10 mM Tris-HCl, pH 7.8 and 0.01% β-mercaptoethanol. This mixture was sonicated and centrifuged at 137,000*g* for 30 min at 4 ^{o}C. The supernatant was diluted two-fold with high salt loading buffer (25 mM Tris-HCl, 1 M NaCl, 5 mM $CaCl_2$, pH 7.8) and dialyzed three times to facilitate refolding. After dialysis, the insoluble precipitate was removed by centrifugation at 142,000*g* for 1 hr at 4 ^{o}C. The soluble fraction was purified over a mannose Sepharose column using 1 M NaCl, 25 mM Tris-HCl, 5 mM ethylenediaminetetraacetic acid (EDTA) at pH 7.8 as an eluent. Purified protein was diluted into low salt loading buffer (LSLB) (25 mM Tris-HCl, 125 mM NaCl, 5 mM $CaCl_2$, pH 7.8) and concentrated with an Amicon Ultra-15 10k NMWL centrifugal filter device (Millipore). Protein concentrations were determined by Bradford Assay (Promega).

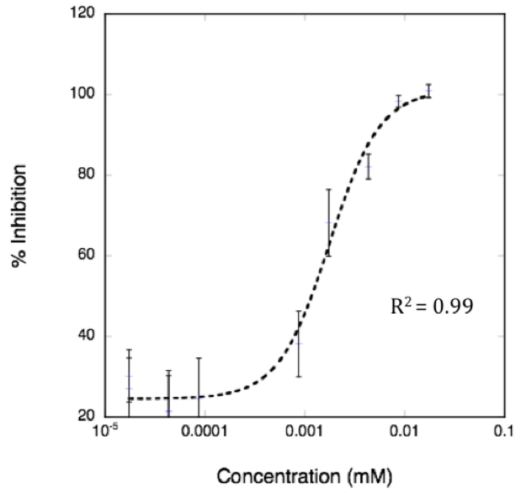
S3. DC-SIGN Binding Assay for IC_{50} Determination of Inhibitors

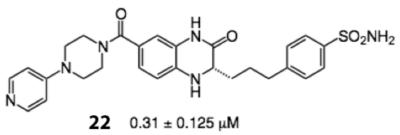
The ECD of DC-SIGN was immobilized onto black Polysorb 384-well plates (Nunc) overnight at 4 ^{o}C (25 μL/well, 200 μg/mL). Plates were washed with low salt loading buffer (LSLB) and then blocked with 2% bovine serum albumin (BSA) in LSLB (50 μL/well) for 2 h. Plates were washed once more with LSLB and then exposed to 20 μL of a fluorescent mannosylated glycoconjugate (bovine serum albumin modified with α-D-mannopyranosyl phenyl isothiocyanate and fluorescein isothiocyanate, Sigma; 20 μg/mL) probe in 2% BSA-LSLB containing 0.005% Triton-X to prevent aggregation of the compounds. Compounds were dissolved in 1 μL of DMSO solution at the given concentrations and added to the wells. After 1 h, plates were washed three times with LSLB, and the fluorescence emission was determined using a Wallac Envision plate reader (Perkin-Elmer) at an excitation wavelength of 480 nm and an emmision wavelength of 520 nm. The concentration required for 50% inhibition (IC_{50}) was determined using data from 5 replicates per compound tested. Data were fit using the Hill-Slope equation assuming a 1:1 binding stoichiometry of compound to protein.



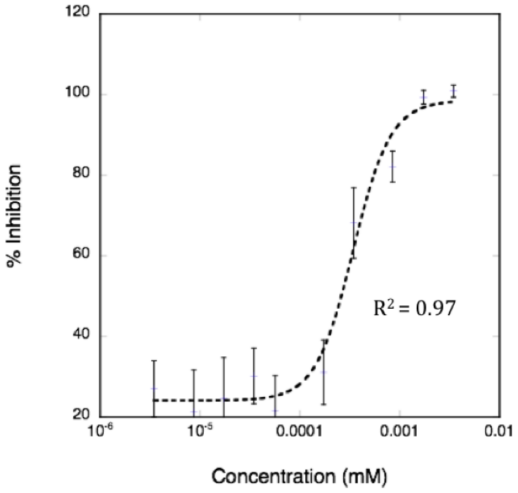


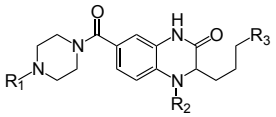
22 1.31 ± 0.234 μM

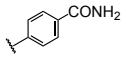
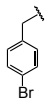
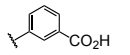
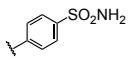
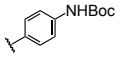
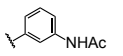
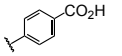
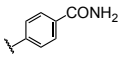
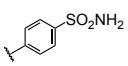




22 0.31 ± 0.125 μM

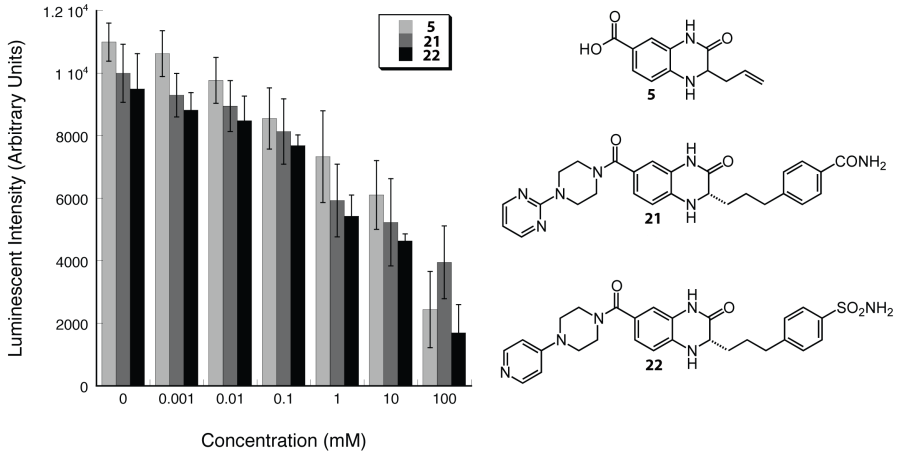




R_1	R_2	R_3	IC_{50} (μM)	R_1	R_2	R_3	IC_{50} (μM)
Me	Me	Me	329 ± 65.8	Ph	H		71 ± 11
Me	H	Me	313 ± 47.7				
Boc	Et	Me	302 ± 43.8		Et		68 ± 11
Boc	H	Me	280 ± 40.6				
Boc	H		270 ± 44.8		H		54 ± 8.1
Ph	Me	Me	260 ± 36.4				
Ph	Me	Ph	240 ± 31.2		Bn		39 ± 6.2
Ph	Bn		170 ± 23.8		H		28 ± 3.9
Ph	H	Ph	155 ± 18.6				
	Me	Ph	150 ± 24.8		H		23 ± 3.4
	H	Ph	113 ± 20.4		H		10 ± 1.3
	H	Ph	110 ± 17.6		H		2.6 ± 0.28
Ph	H		84 ± 13		H		0.31 ± 0.13

S4. Raji Cell Cytotoxicity Measurements

The cytotoxicity of the compounds was ascertained using Raji cells (a human Burkitt's lymphoma cell line, American Type Tissue Culture) using the CellTiter-Glo luminescent cell viability assay (Promega). Raji cells were grown to a confluence of 500,000 cells/mL in cRPMI media containing 10% fetal bovine serum (FBS), 0.5% L-glutamate and 1% penicillin/streptomycin. A portion of the cell suspension (100 μL) of the cell suspension was added to clear luminescent 96-well plates (Nunc). To this was added 1 μL of compound dissolved in DMSO. The cells were kept at 37 ^{o}C in a 5% CO_2 atmosphere for 24 hr. CellTiter-Glo Reagent (100 μl) was added and the wells incubated at rt for 30 min. The amount of cell death was determined by luminescence intensity on a Tecan Ultra 384 plate reader. Measurements represent an average of three trials. Error bars represent the standard deviation of three replicates.



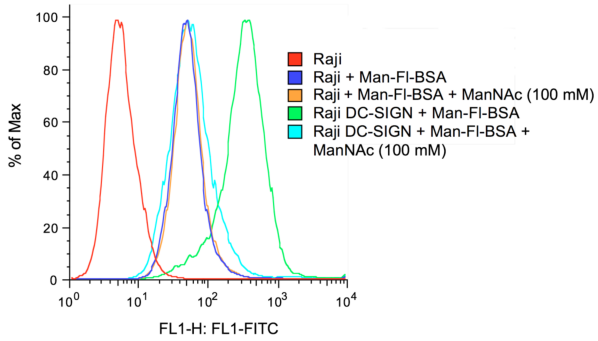
S5. DC-SIGN Transfection of Raji Cells and Microscopy

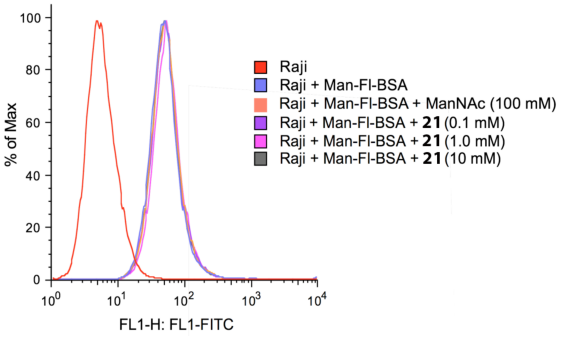
Raji cells transfected with the extracellular domain of DC-SIGN, as well as the parental, untransfected strain, were obtained through the NIH AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH: Raji/DC-SIGN from Drs. Li Wu and Vineet N. KewalRamani.[2] Cells were maintained in cRPMI media containing 10% FBS, 0.5% L-glutamate, and 1% penicillin/streptavidin. Prior to microscopy, Raji cells were spun at 1100 rpm and the supernatant removed. The cells were resuspended in phosphate buffer saline (PBS, pH 8.0) containing 1% BSA and 1 mM $CaCl_2$ to a final concentration of 500,000 cells/mL. To 200 μL of cells was added 20 μL of the DC-SIGN specific antibody AZND1-PE (Beckman Coulter). The cells were incubated at 37 ^{o}C for 15 min, washed, and analyzed by microscopy. Images were collected using an inverted Nikon A1R Eclipse Ti-E confocal microscope with a 60x (1.4 NA) oil immersion lens. Images were processed using Adobe Photoshop CS2 (brightness adjusted using autolevels, color converted to RGB, overlaid.)

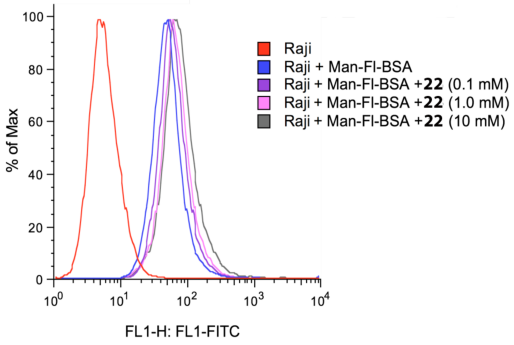
[2] Wu, L.; Martin, T.D.; Carrington, M.; KewalRamani V.N. *Virology*, **2004**, 318, 17-23.

S6. Flow Cytometry

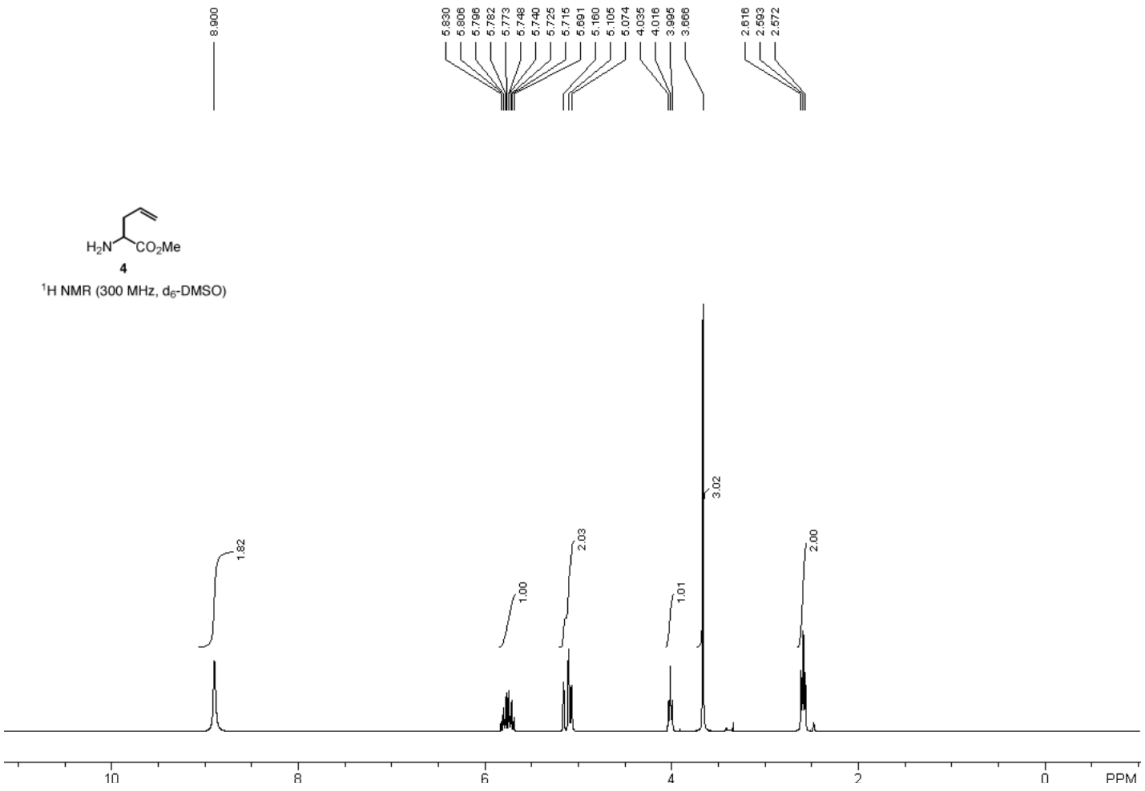
Stably transfected DC-SIGN Raji cells were maintained in cRPMI medium containing 10% FBS, 0.5% L-glutamate, and 1% penicillin/streptavidin. The cells were spun at 1100 rpm and the supernatant removed. The cells were resuspended in phosphate buffer saline (PBS, pH 8.0) containing 1% BSA and 1 mM $CaCl_2$ to a final concentration of 500,000 cells/mL. For the surface expression experiments, 20 μL antibody DCN46-FITC (BD Biosciences) was added to 200 μL cells. Cells were cooled on ice for 30 minutes and washed with PBS containing 1% BSA. For the blocking experiments, to 200 μL of cells was added mannose-functionalized BSA (Sigma) conjugated with Alexafluor 488 (10 μL, 14 μg/mL; Invitrogen) in PBS buffer. N-Acetylmannosamine (ManNAc) was dissolved in PBS to a final concentration of 100 mM. Compounds **11** and **13** were dissolved in PBS at concentrations ranging from 0.10-10 mM. 20 μL of each compound was added and the cells were allowed to incubate at 37 °C for 35 min. The cells were pelleted and resuspended in 800 μL of phosphate buffer saline (PBS, pH 8.0) containing 1% BSA. The extent of binding and internalization was measured by flow cytometry. The percentage inhibition was determined from geometric means normalized to the values obtained from Raji DC-SIGN producing cells with no inhibitor present. Flow cytometry was performed on a Becton Dickinson (BD) FACSCalibur flow cytometer. Data were analyzed using Flowjo 9.1 (Tree Star, Inc).

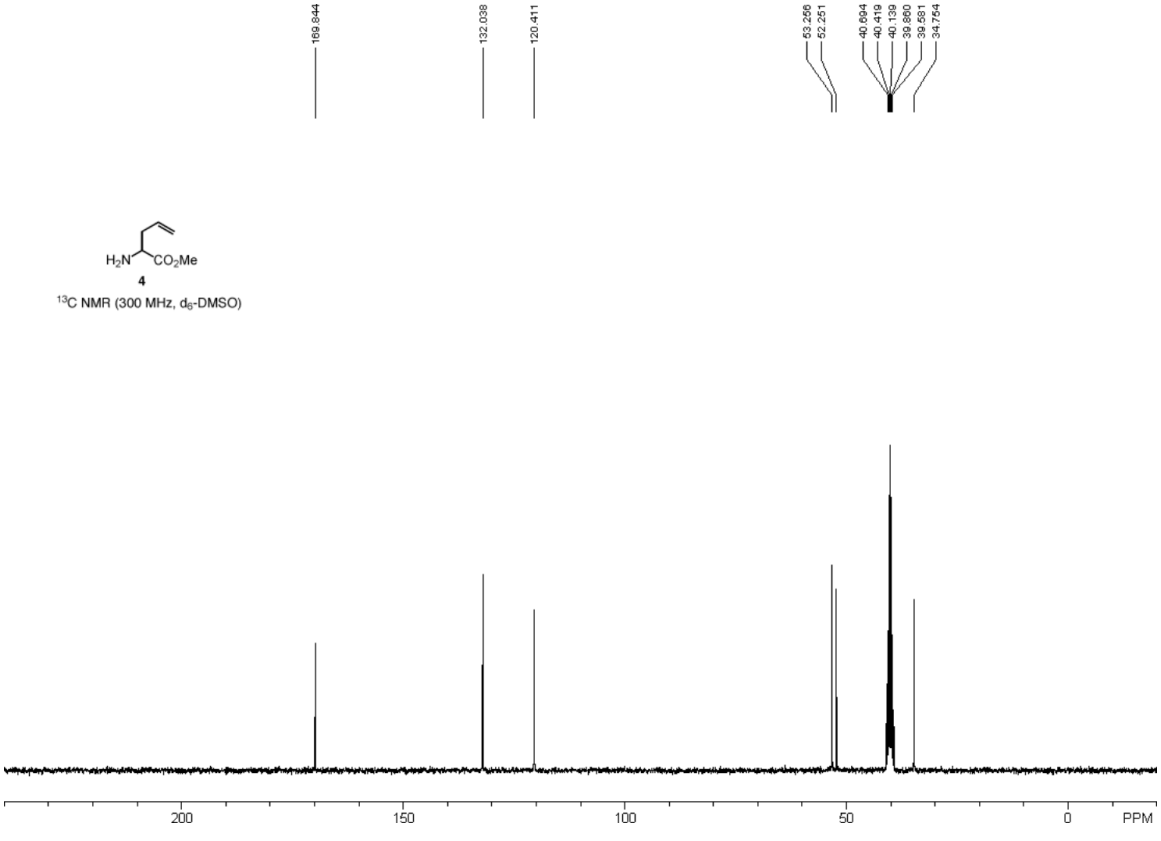


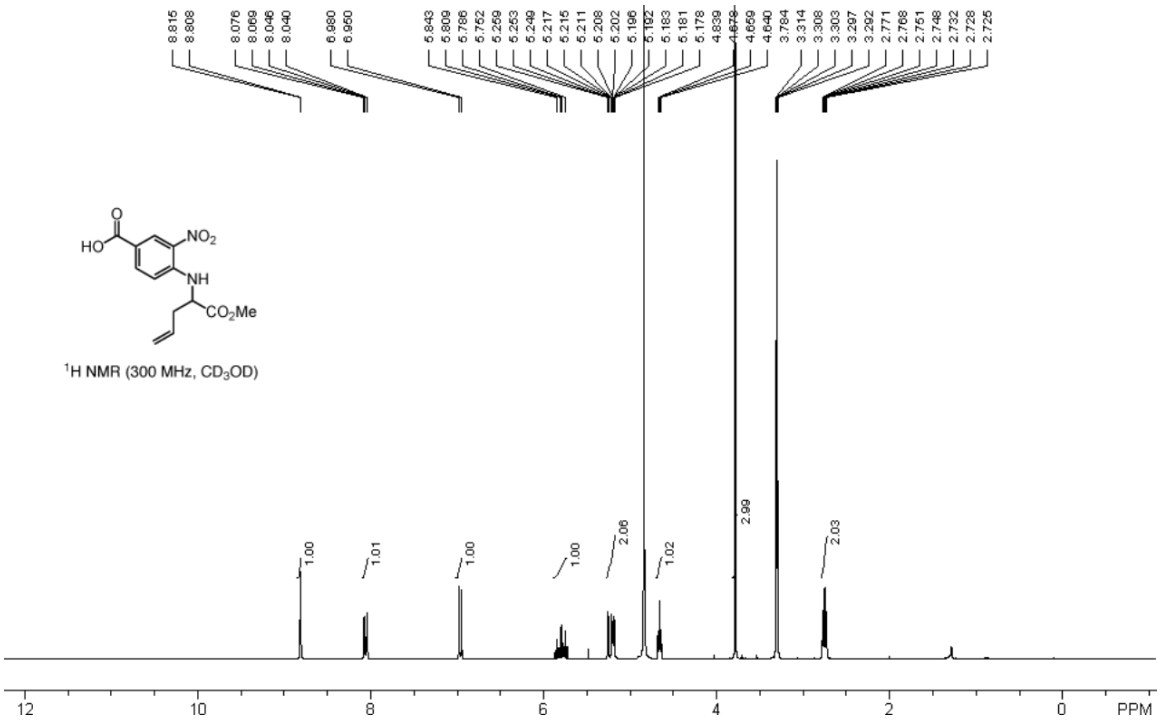




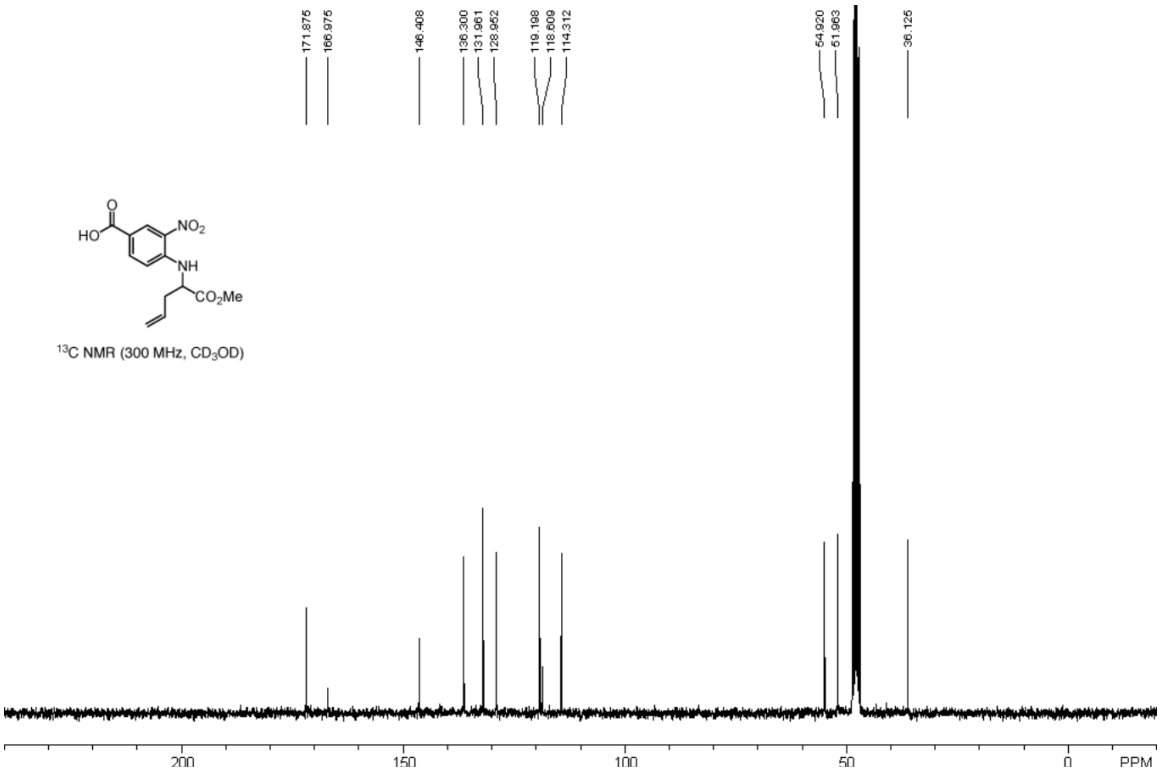
S8. NMR Spectra



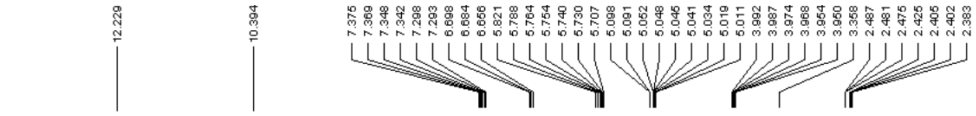


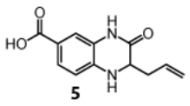


^{1}H NMR (300 MHz, CD_3OD)



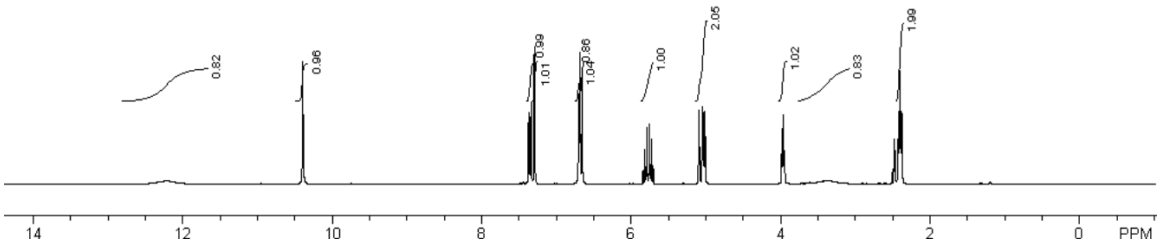
^{13}C NMR (300 MHz, CD_3OD)

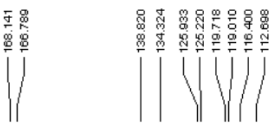


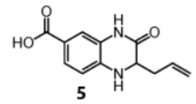


5

^{1}H NMR (300 MHz, d_6-DMSO)







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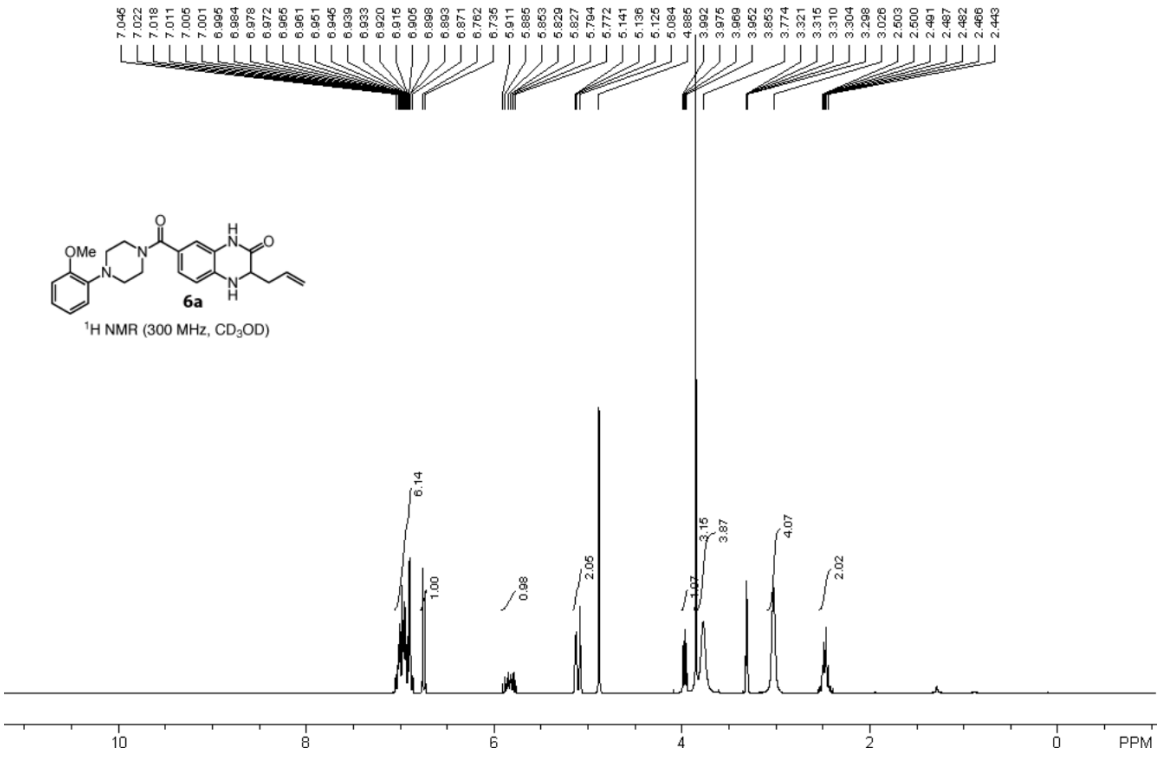
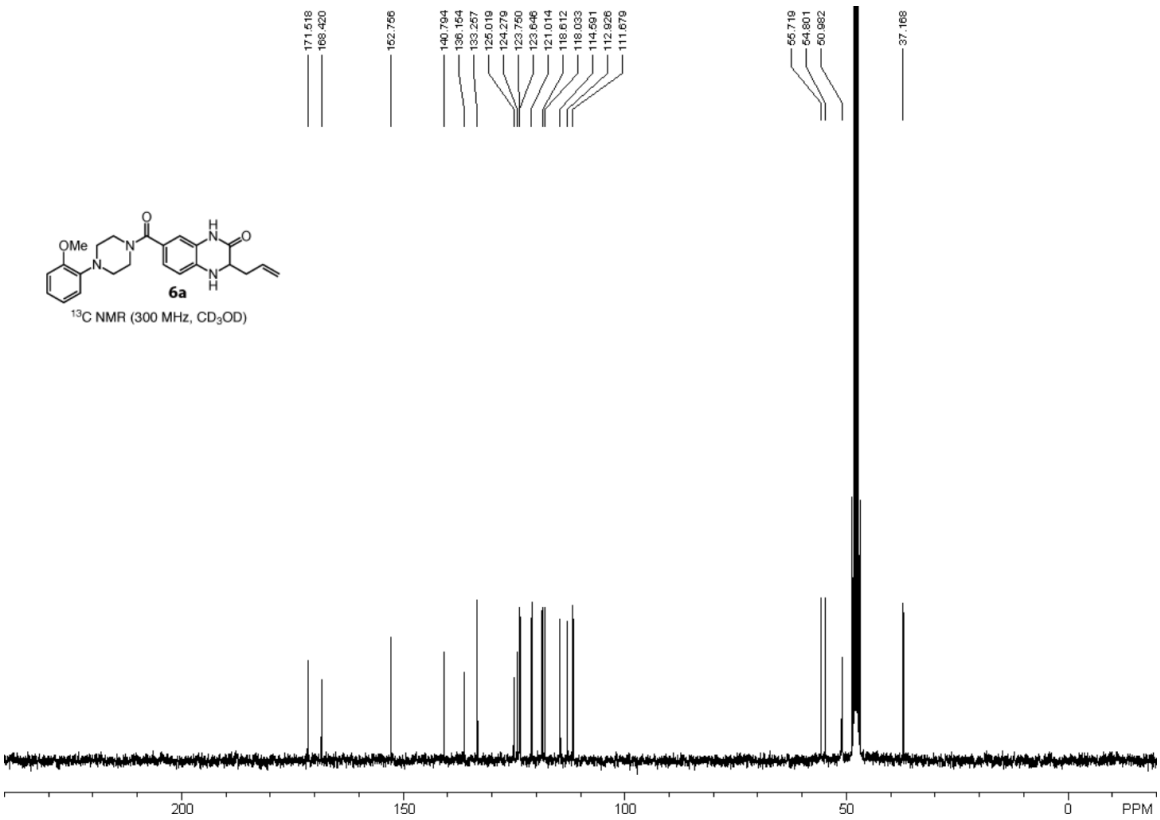
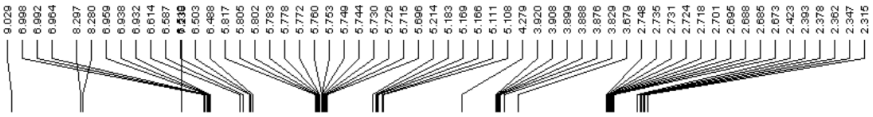
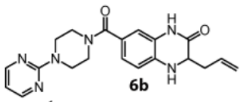
^{13}C NMR (300 MHz, d_6-DMSO)

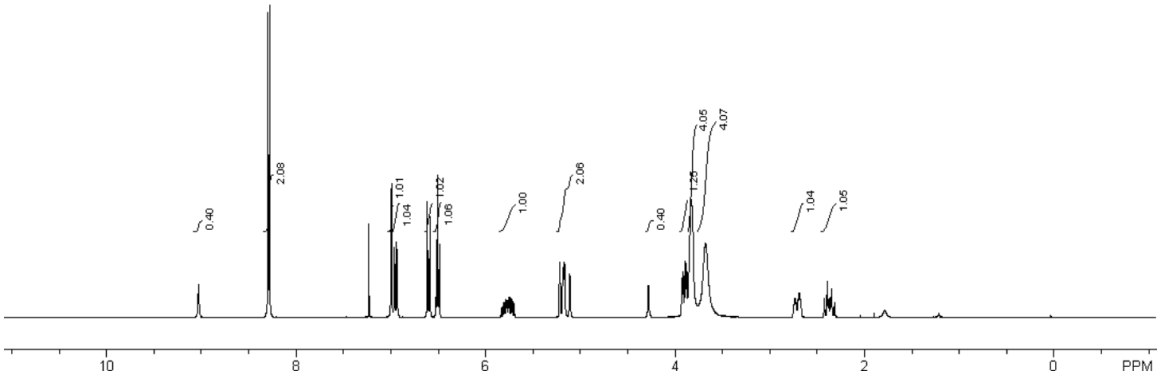


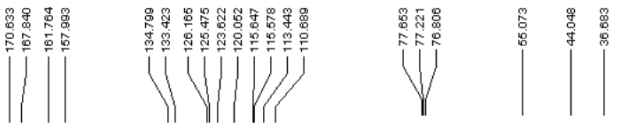


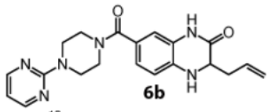




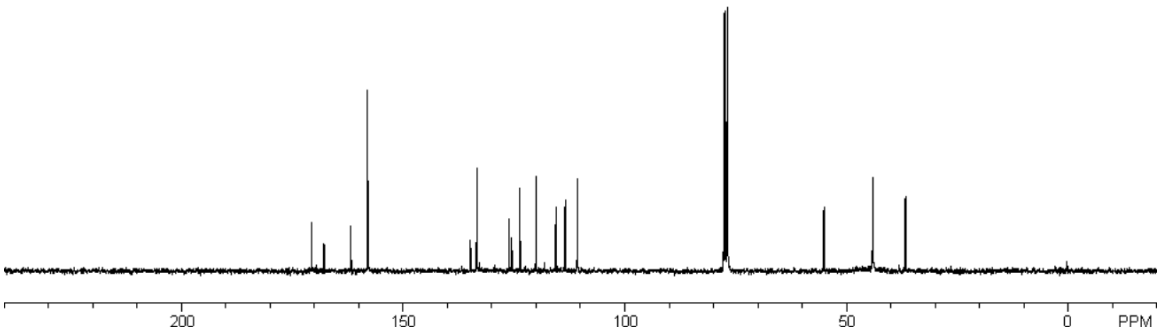
^{1}H NMR (300 MHz, $CDCl_3$)

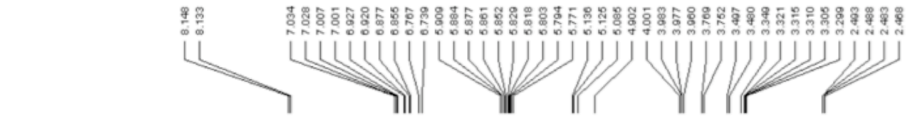


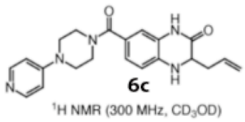




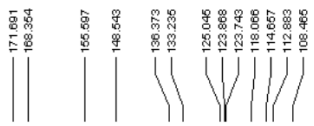
^{13}C NMR (300 MHz, $CDCl_3$)

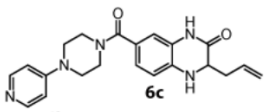




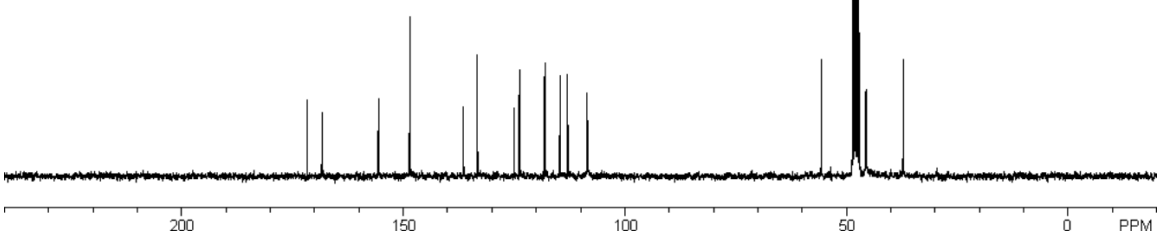


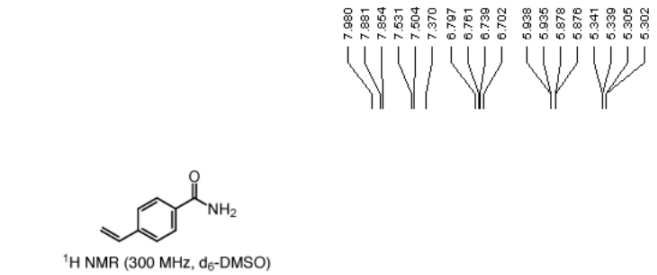
^{1}H NMR (300 MHz, CD_3OD)



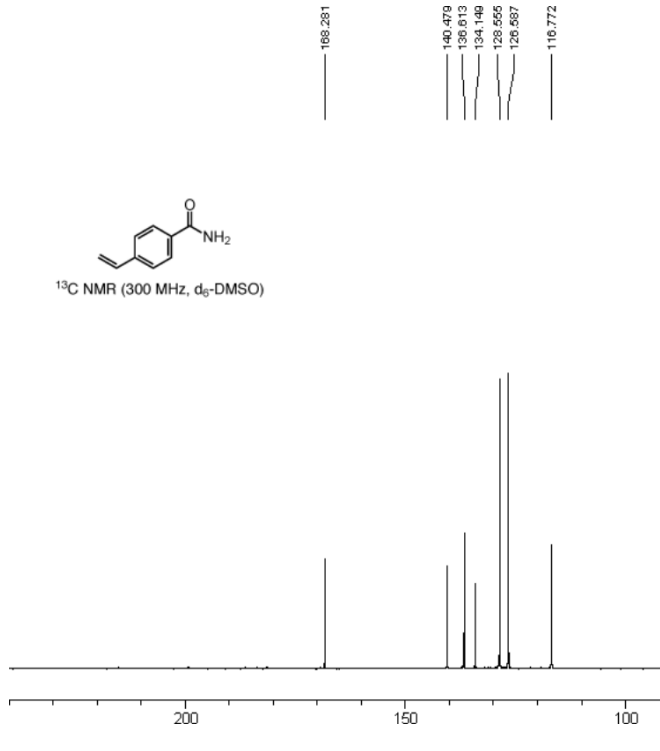


^{13}C NMR (300 MHz, CD_3OD)

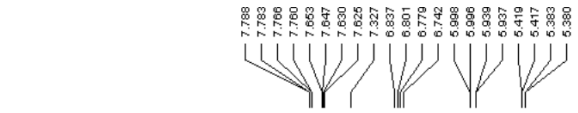


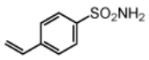


^{1}H NMR (300 MHz, d_6-DMSO)

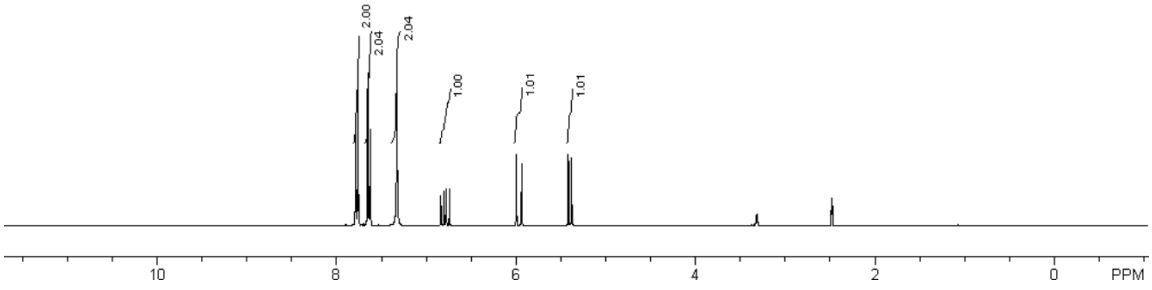


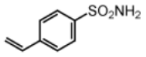
^{13}C NMR (300 MHz, d_6-DMSO)



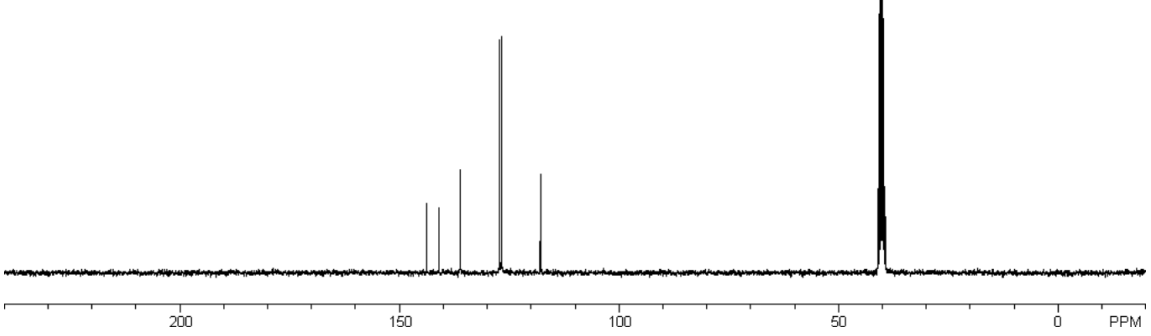


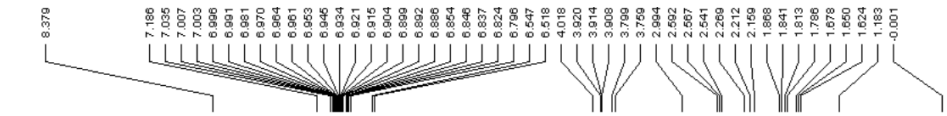
^{1}H NMR (300 MHz, d_6-DMSO)

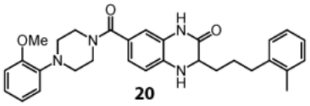




^{13}C NMR (300 MHz, d_6-DMSO)







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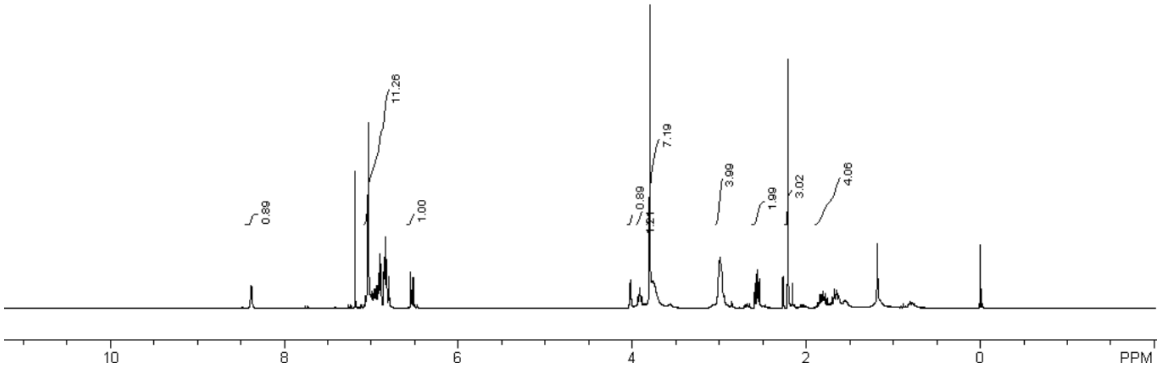
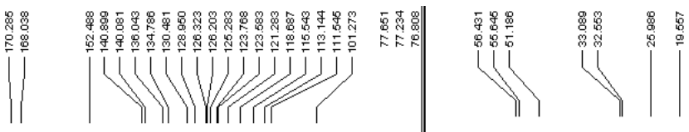
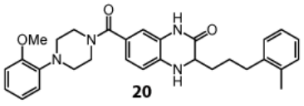
^{1}H NMR (300 MHz, $CDCl_3$)







20

^{13}C NMR (300 MHz, $CDCl_3$)