Supporting Information

The Di-Aryl Sulfonamide Motif Adds π-Stacking Bulk in Negative Allosteric Modulators of the NMDA Receptor

Samantha L. Summer[†], Steven A. Kell[†§], Zongjian Zhu[§], Rhonda Moore[†], Dennis C. Liotta[*†], Scott J. Myers[‡§], George W. Koszalka[‡], Stephen F. Traynelis[*§], David S. Menaldino[*†]

†Department of Chemistry, Emory University, Atlanta, GA 30322

§Department of Pharmacology, Emory University School of Medicine, Atlanta, GA 30322

‡NeurOp Inc., 58 Edgewood Avenue, Atlanta, GA 30303

Biology Experimental Section

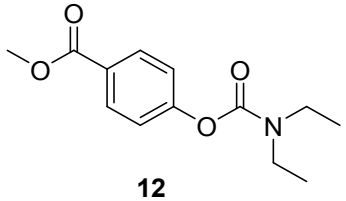
Unfertilized *Xenopus laevis* oocytes were obtained from Ecocyte (Austin, TX). Two-electrode voltage-clamp recordings were performed on oocytes expressing recombinant rat GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, or GluN1/GluN2D. cDNAs for rat GluN1-1a (GenBank accession numbers U11418 and U08261) GluN2A (D13211), GLuN2B (U11419), GluN2C (M91563), and GluN2D (D13213) were provided by Dr. S. Heinemann from the Salk Institute, Dr. S. Nakanishi from Kyoto University and Dr. P. Seeburg from the University of Hidelberg. GluN2C and GluN2D were modified as previously described.[1] Oocyte isolation, cRNA synthesis, and cRNA injections were performed as previously described.[2] *Xenopus laevis* oocytes were injected with 10 ng of cRNA and incubated at 15-19 °C in Barth's solution consisting of (in mM) 88 NaCl, 1 KCl, 24 $NaHCO_3$, 10 HEPES, 0.82 $MgSO_4$, 0.33 $Ca(NO_3)_2$, and 0.91 $CaCl_2$ and supplemented with 100 μg/mL gentamycin, 40 μg/mL streptomycin, and 50 μg/mL penicillin. Recordings were performed after 2-4 days' injection with extracellular recording solution containing (in mM) 90 NaCl, 1 KCl, 10 HEPES, 0.5 $BaCl_2$, 0.01 EDTA at pH 7.4 adjusted with NaOH. To prevent a gradual increase in current response over the course of the experiment, some oocytes expressing GluN1/GluN2A were injected with 50 nl of 2 mM K-BAPTA. Concentration−response curves for test compounds were generated by applying a maximally effective concentration of glutamate (100 μM) and glycine (30 μM), followed by variable concentrations of test compound up to 100 μM. Test compounds were prepared as 20 mM stock solutions in DMSO, and diluted to the final concentration in recording solution. DMSO content was 0.05−0.5% (v/ v). 2-hydroxypropyl-β-cyclodextrin (1−10 mM) was added to the recording solution for Xenopus oocyte recordings to ensure that the compounds remained in solution. No detectable effect on NMDAR response was observed for 2-hydroxypropyl-β-cyclodextrin alone.

Chemistry Experimental Section

Computational Chemistry:

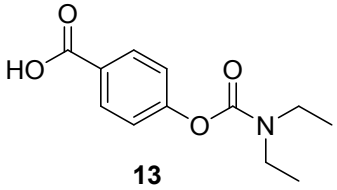
Conformational searches were performed for TCN201 (**9**), TCN201-25 (**23**), 1063-69 (**27**), and 1063-73 (**26**). The conformational search parameters were as follow: 100 steps per rotatable bond of Mixed Torsional/Low-Mode sampling was performed on each of the four compounds using the OPLS3 force field within the MacroModel module of Maestro (Schrödinger Release 2017-1: MacroModel; Schrödinger, LLC, New York, NY). The Generalized Born/Surface Area (GB/SA) H_2O solvation model was used along with a relaxed 30 kJ/mol energy cut-off. To ensure complete energy convergence, the resulting structures were subjected to a maximum of 2500 iterations of Polak-Ribière Conjugate Gradient (PRCG) minimization with a gradient convergence threshold of 0.05. Conformers resulting from the conformational searches were combined and redundant conformations removed using a minimum allowed atom deviation of 0.5-Å. The global minimum was found between three and six times for the different searches, assuring complete coverage of conformational space.

General Chemistry:
All reagents were purchased from commercial vendors and used without further purification. Thin layer chromatography (TLC) on precoated aluminum plates (silica gel 60 F254, 0.25 mm) or LCMS (Varian) were used to monitor reaction progress. Purification by flash column chromatography was done on a Teledyne ISCO Combiflash Companion using Teledyne Redisep normal phase columns. Proton and carbon NMR spectra were recorded on an INOVA-500 (500MHz) or Bruker Ascend 600 (600 MHz), All chemical shifts were reported in parts per million, and coupling constants were reported in hertz (Hz). The spectra were referenced to the solvent peak. Mass spectra were performed by the Emory University Mass Spectroscopy Center on either a VG 70-S Nier Johnson or JEOL instrument. Purity was established by LC-MS (Varian) in a MeOH:water solvent system and were shown to be greater than 95% pure by two different methods.



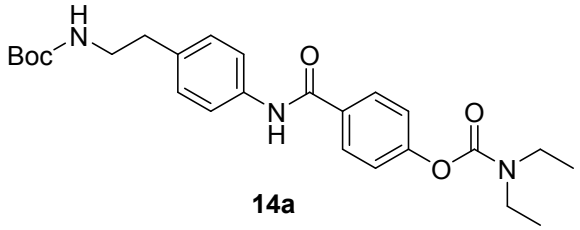
12

Methyl 4-((diethylcarbamoyl)oxy)benzoate (12): Methyl 4-hydroxybenzoate (1.0g, 6.57mmol) and finely ground potassium carbonate (1.82g, 13.15mmol, 2.0eq) were dissolved in DMF (25.3mL). The mixture stirred at room temperature for 1 hour to give an opaque suspension. Diethylcarbamoyl chloride (0.92mL, 7.23mmol, 1.1eq) was then added and the reaction mixture stirred at room temperature for 12 hours or until complete by TLC/LCMS. The reaction mixture was diluted with water and extracted twice with diethyl ether. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to yield 0.90g (54.5% yield) of **12** as a clear colorless liquid. The product was carried forward in the next reaction without purification.



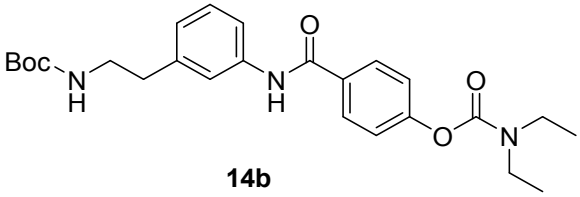
13

4-((Diethylcarbamoyl)oxy)benzoic acid (13): To a solution of methyl 4-((diethylcarbamoyl)oxy) benzoate (7.98g, 31.8mmol) in methanol (63.5mL), 2M sodium hydroxide (60.3mL, 121mmol, 3.8eq) was added. A solid formed within a few minutes and the reaction mixture stirred at rt for 12 hours until it became homogeneous. The pH of the mixture was adjusted to approximately 3 with 6M HCl. The methanol was removed in vacuo and the aqueous mixture was stored at 4°C for a few hours until a precipitate formed. The solids were collected by vacuum filtration and washed with hexanes to yield the title compound (**13**, 6.25g), in 83% yield as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 7.98 – 7.92 (m, 2H), 7.25 – 7.20 (m, 2H), 3.33 (dq, *J* = 47.0, 7.1 Hz, 4H), 1.14 (dt, *J* = 37.3, 7.1 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d6) δ 167.14, 155.26, 153.13, 131.13, 127.91, 122.27, 115.54, 42.27, 42.04, 14.60, 13.66. HRMS calcd for $C_{12}H_{16}NO_4$, 238.10738 $[M+H]^+$; found 238.10762.



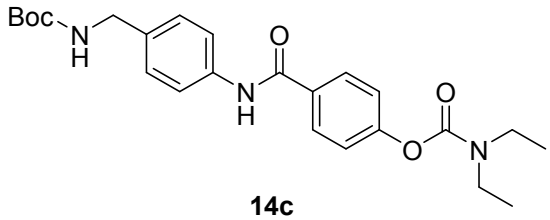
14a

4-((4-(2-((*tert*-Butoxycarbonyl)amino)ethyl)phenyl)carbamoyl)phenyl diethylcarbamate (14a): 4-((Diethylcarbamoyl)oxy)benzoic acid (**13**, 4.0g, 16.86mmol) was dissolved in DCM (84mL) and cooled to 0°C. To this solution, N,N-diisopropylethylamine (8.8mL, 50.58mmol, 3.0eq), HATU (7.69g, 20.23mmol,1.2eq) were added, followed by the addition of were added. *tert*-butyl 4-aminophenethylcarbamate (4.78g, 20.23mmol, 1.2eq) was added. The reaction mixture was warmed to room temperature and stirred for 12 hours at which is was shown complete by TLC. Upon completion, the reaction is diluted with water The organic layer was separated, washed with 1N HCl and brine, dried over anhydrous sodium sulfate and concentrated in vacuo to yield the title compound, (**14a**, 4.64g, 60.4% yield) as a yellow solid. The crude product was carried forward in the next step without further purification.



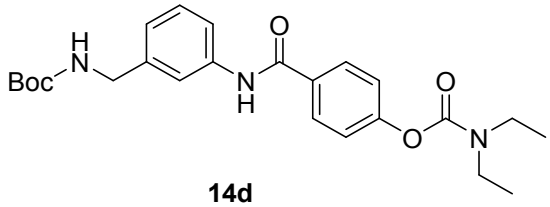
14b

4-((3-(2-((*tert*-Butoxycarbonyl)amino)ethyl)phenyl)carbamoyl)phenyl diethylcarbamate (14b): To a solution of 4-(diethylcarbamoyloxy)benzoic acid (**13**, 1.0g, 4.21mmol) in dichloromethane (8.4mL) was added N,N-diisopropylethylamine (2.2mL, 12.64mmol, 3.0eq), HATU (1.92g, 5.06mmol, 1.2eq) , and *tert*-butyl N-[2-(3-aminophenyl)ethyl]carbamate (1.2g, 5.06mmol, 1.2eq). The reaction was stirred at rt overnight until complete by TLC/LCMS. The reaction mixture was then diluted with water, and the organic layer was washed twice with 1N HCl, once with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to yield the title compound (**14b**, 1.19g, 61.7% yield) as a yellow solid. The crude product is carried forward in the next step without further purification.



14c

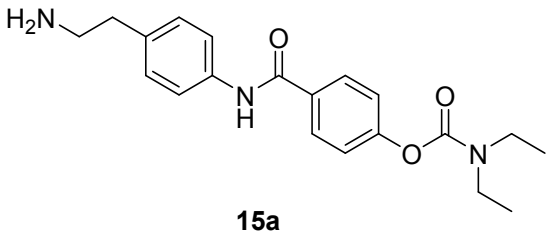
4-((4-(((*tert*-Butoxycarbonyl)amino)methyl)phenyl)carbamoyl)phenyl diethylcarbamate (14c): To a cooled solution of 4-((diethylcarbamoyl)oxy)benzoic acid (**13**, 1.48g, 6.26mmol) in anhydrous DMF (20mL) at 0°C under Argon atmosphere were added dimethylaminopyridine (0.84g, 6.89mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.2g, 6.26mmol). The mixture was stirred for 30 minutes at 0°C, then *tert*-butyl (4-aminobenzyl)carbamate (1.53g, 6.89mmol) was added and the resulting mixture was allowed to warm to rt overnight. After concentrating the mixture to half volume on a roto-evaporator, the mixture was transferred to a separatory funnel, partitioned between ethyl acetate (100mL) and chilled 1N HCl (20mL) and the layers separated. The aqueous layer was re-extracted with EtOAc (50mL), and the combined organic layers washed with 50% brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give 2.85g of a clear sticky oil. Purification on silica using 0-20% ethyl acetate in hexanes to produce the title compound (**14c**, 2.2g, 79% yield) as a white fluffy solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.88 – 7.81 (m, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.30 – 7.25 (m, 3H), 7.23 – 7.15 (m, 2H), 4.86 (s, 1H), 4.29 (d, J = 5.9 Hz, 2H), 3.43 (dq, J = 25.8, 7.1 Hz, 4H), 1.62 (s, 2H), 1.47 (s, 9H), 1.25 (dt, J = 25.0, 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.04, 154.27, 153.61, 137.17, 131.58, 128.34, 128.20, 121.94, 120.40, 42.36, 42.00, 28.41, 14.24, 13.35. HRMS calcd for $C_{24}H_{32}O_5N_3$, 442.23365 $[M+H]^+$; found 442.23414.



14d

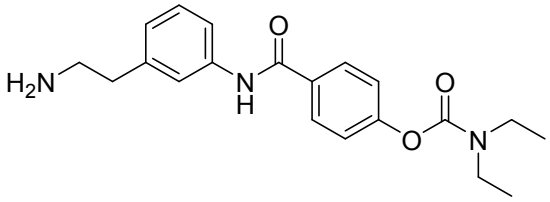
4-((3-(((*tert*-Butoxycarbonyl)amino)methyl)phenyl)carbamoyl)phenyl diethylcarbamate (14d): To a cooled solution of 3-((diethylcarbamoyl)oxy)benzoic acid (**13**, 0.48g, 2.06mmol) in anhydrous DMF (10mL) at 0°C under Argon atmosphere were added dimethylaminopyridine (0.27g, 2.25mmol, 1.1eq) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.39g, 2.06mmol, 1.0eq). The mixture was stirred for 30 minutes at 0°C, then *tert*-butyl (3-aminobenzyl)carbamate (0.50g, 2.25mmol, 1.1 eq) was added and the resulting mixture was allowed to warm to rt overnight. After concentrating the mixture to half volume on a rotary evaporator, the mixture was transferred to a separatory funnel, partitioned between ethyl acetate (50mL) and chilled 1N HCl (10mL) and the layers separated. The aqueous layer was re-extracted with EtOAc (25mL), and the combined organic layers washed with 50% brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give 0.96g of a clear sticky oil. Purification on silica using 0-20% ethyl acetate in hexanes produced the title compound (**14d**, 0.8g, 89% yield) as a white fluffy solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 6.1 Hz, 1H), 7.79 (ddd, J = 7.8, 5.1, 2.3 Hz, 2H), 7.56 (s, 1H), 7.51 (dd, J = 6.8, 4.0 Hz, 1H), 7.31 – 7.23 (m, 1H), 7.19 – 7.08 (m, 2H), 7.03 (t, J = 6.7 Hz, 1H), 5.03 (d, J = 10.8 Hz, 1H), 4.25 (s, 2H), 3.42 (dq, J = 25.3, 7.3 Hz, 4H), 1.45 (t, J = 2.2 Hz, 9H), 1.24 (dt, J = 24.8, 7.2 Hz, 6H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 165.28, 155.98, 154.11, 153.73, 139.81, 138.44, 131.59, 129.12, 128.51, 123.38, 121.76, 119.37, 44.57, 42.36, 42.02, 28.41, 14.23, 13.36. HRMS calcd for $C_{24}H_{30}O_5N_3$, 440.21909 $[M-H]^-$; found 440.21915.



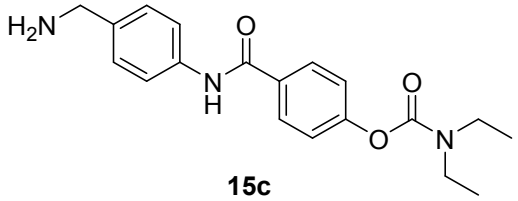
15a

4-((4-(2-Aminoethyl)phenyl)carbamoyl)phenyl diethylcarbamate (15a): To a solution of 4-((4-(2-((tert-butoxycarbonyl)amino)ethyl)phenyl)carbamoyl)phenyl diethylcarbamate (**14a**, 4.64g, 10.18mmol) in DCM (30.0mL), TFA (3mL, 40.74mmol, 4eq) was added. The reaction was monitored by TLC. Upon completion, the reaction mixture was basified at 0°C using 1N sodium hydroxide to pH 10 and extracted three times with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to yield the title compound (**15a**, 3.3g, 91.2%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.26 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 3.35 (dq, *J* = 49.8, 7.1 Hz, 4H), 2.88 (dd, *J* = 8.6, 6.6 Hz, 2H), 2.72 (dd, *J* = 8.8, 6.4 Hz, 2H), 1.15 (dt, *J* = 41.4, 7.1 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d6) δ 165.09, 154.20, 153.32, 137.88, 134.63, 132.07, 129.41, 129.20, 122.10, 120.93, 42.43, 42.25, 42.01, 36.60, 14.62, 13.68. HRMS calcd for $C_{20}H_{26}N_3O_3$, 356.19687 $[M+H]^+$; found 356.19623



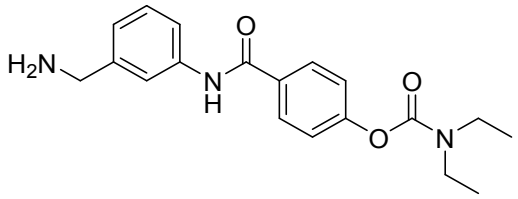
15b

4-((3-(2-Aminoethyl)phenyl)carbamoyl)phenyl diethylcarbamate (15b): To a solution of [4-[[3-[2-(tert-butoxycarbonylamino)ethyl]phenyl]carbamoyl]phenyl] N,N-diethylcarbamate (**14b**, 3.0g, 6.59mmol) in DCM (5mL) at 0°C was added TFA (5.0mL, 64.9mmol, 10eq). The reaction was stirred at room temperature until complete by TLC/LCMS, then basified to pH 10 with 2N NaOH. The mixture is extracted three times with DCM, the organic phase dried over anhydrous sodium sulfate and concentrated in vacuo. The residue is purified via silica gel column chromatography to yield the title compound (**15b**,1.6g, 68.4% yield) as a yellow oil. ^{1}H NMR (600 MHz, CD_3OD) δ 7.99 – 7.93 (m, 2H), 7.62 (d, *J* = 1.8 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.27 – 7.21 (m, 2H), 7.04 (dt, *J* = 7.6, 1.3 Hz, 1H), 3.43 (dq, *J* = 60.7, 7.1 Hz, 4H), 3.04 (dd, *J* = 8.3, 6.7 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 1.23 (dt, *J* = 46.6, 7.1 Hz, 6H). ^{13}C NMR (151 MHz, CD_3OD) δ 220.74, 183.95, 172.47, 166.56, 154.21, 154.02, 147.17, 138.72, 138.64, 131.69, 128.82, 128.68, 124.68, 121.52, 121.36, 119.43, 109.99, 50.82, 42.14, 41.89, 41.43, 35.66, 13.10, 12.18, 3.41. HRMS calcd for C20H26O3N3, 356.19687 $[M+H]^+$; found 356.19707.



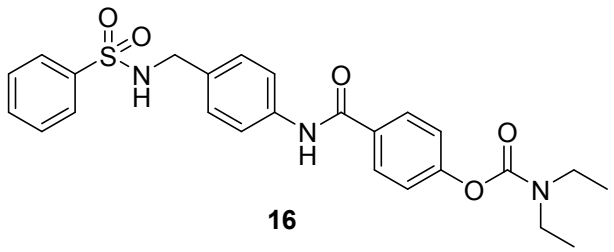
15c

4-((4-(Aminomethyl)phenyl)carbamoyl)phenyl diethylcarbamate (15c): To a cooled (0°C) solution of 4-((4-(((tert-butoxycarbonyl)amino)methyl)phenyl)carbamoyl)phenyl diethylcarbamate (**14c**, 1.0g, 2.26mmol) in dioxane (10mL) was added a 4N HCl solution in dioxane (5.7mL, 22.65mmol, 10eq). The resulting stirred mixture was allowed warm to rt overnight, stirred for 36h, and concentrated. The resulting residue was dissolved in ethyl acetate (150mL), and basified to pH~9 with 0.5N NaOH solution. The layers were then separated, the aqueous layer re-extracted with ethyl acetate (3 x 20mL), and the combined organics washed with 50% brine, dried over Na_2SO_4, filtered, and concentrated to produce the crude product (770mg, quant.) as a thick brown oil. The product was then purified on silica gel using 0-70% 95:5:0.5% DCM:MeOH:NH_4OH in DCM to produce the title compound (**15c**, 0.58g, 58% yield), as thick colorless oil. The product was used without further purification.



15d

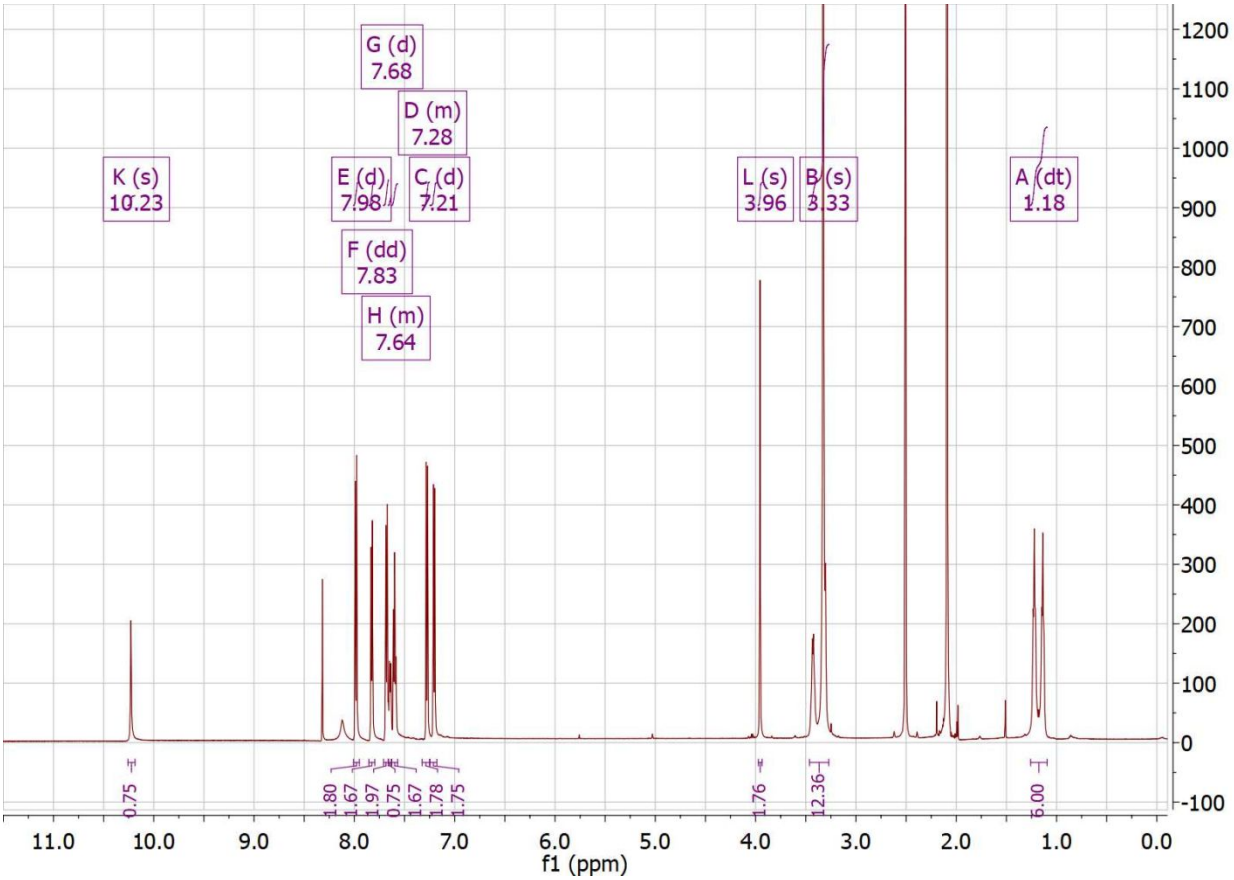
4-((3-(Aminomethyl)phenyl)carbamoyl)phenyl diethylcarbamate (15d): To a cooled (0°C) solution of 4-((3-(((tert-butoxycarbonyl)amino)methyl)phenyl)carbamoyl)phenyl diethylcarbamate (**14d**, 0.65g, 1.47mmol) in dioxane (8mL) was added a 4N HCl solution in dioxane (7.3mL, 29.4mmol). The resulting stirred mixture was allowed warm to rt overnight, stirred for 36h, and concentrated. The resulting residue was dissolved in EtOAc (100mL), and basified to pH~9 with 0.5N NaOH solution. The layers were then separated, the aqueous layer re-extracted with EtOAc (3 x 30mL), and the combined organics washed with 50% brine, dried over Na2SO4, filtered, and concentrated to produce a think oil (500mg, quant) as a thick brown oil. The crude product was then purified on silica gel using 0-70% 95:5:0.5% DCM:MeOH:NH_4OH in DCM to produce the title comound (**15d**, 0.40g, 80% yield), as thick colorless oil. The product was used without further purification.

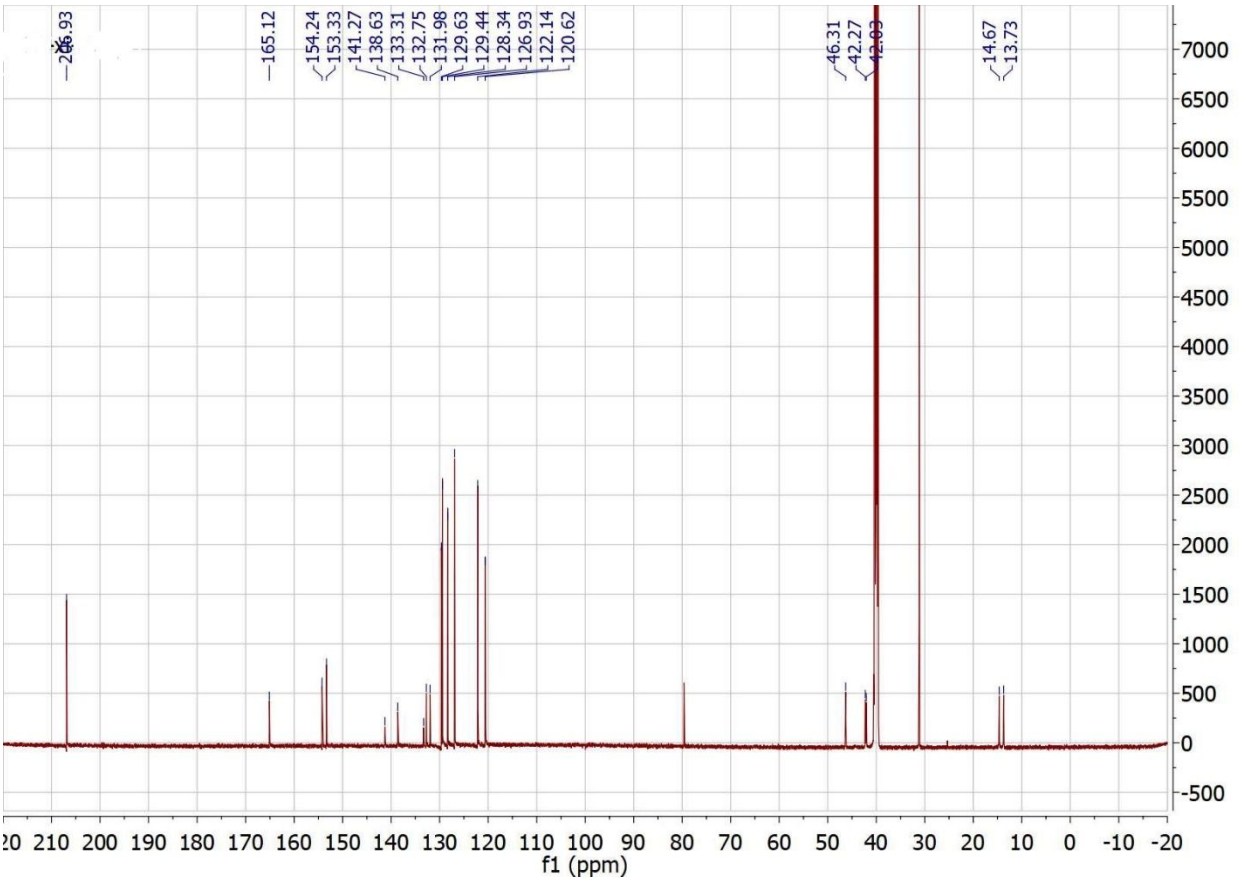


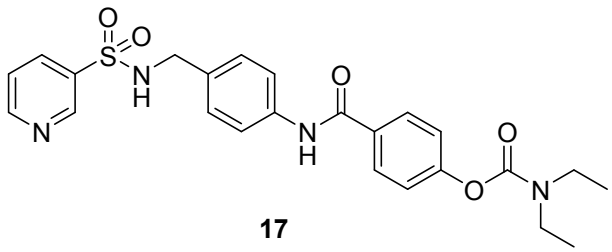
16

4-((4-(Phenylsulfonamidomethyl)phenyl)carbamoyl)phenyl diethylcarbamate (16): To a solution of 4-((4-(aminomethyl)phenyl)carbamoyl)phenyl diethylcarbamate (**15c**, 0.043g,

0.13mmol) in dry ACN (5mL) were added triethylamine (0.052g, 0.77mmol, 6eq), and benzenesulfonylchloride (0.034g, 0.19mmol, 1.5eq) and the resulting mixture was allowed to stir at rt for 36h. The crude reaction mixture was then partitioned between EtOAc (25mL) and 0.25N HCl solution (10mL). The aqueous layer was re-extracted with EtOAc and the combined organics were washed with sat. $NaHCO_3$ solution, 50% brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 80mg of an off-white solid. The crude materials is purified on silica using 0-50% EtOAc in hexanes to produce the title compound (**16**, 40mg, 64% yield) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d6) δ 10.23 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.83 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.66 – 7.63 (m, 1H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.32 – 7.25 (m, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 3.96 (s, 2H), 3.33 (s, 4H + water), 1.18 (dt, *J* = 50.9, 7.2 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d6) δ 206.93, 165.12, 154.24, 153.33, 141.27, 138.63, 133.31, 132.75, 131.98, 129.63, 129.44, 128.34, 126.93, 122.14, 120.62, 46.31, 42.27, 42.03, 14.67, 13.73.HRMS calcd for $C_{25}H_{28}O_5N_3S$, 482.17442 $[M+H]^+$; found 482.17492.



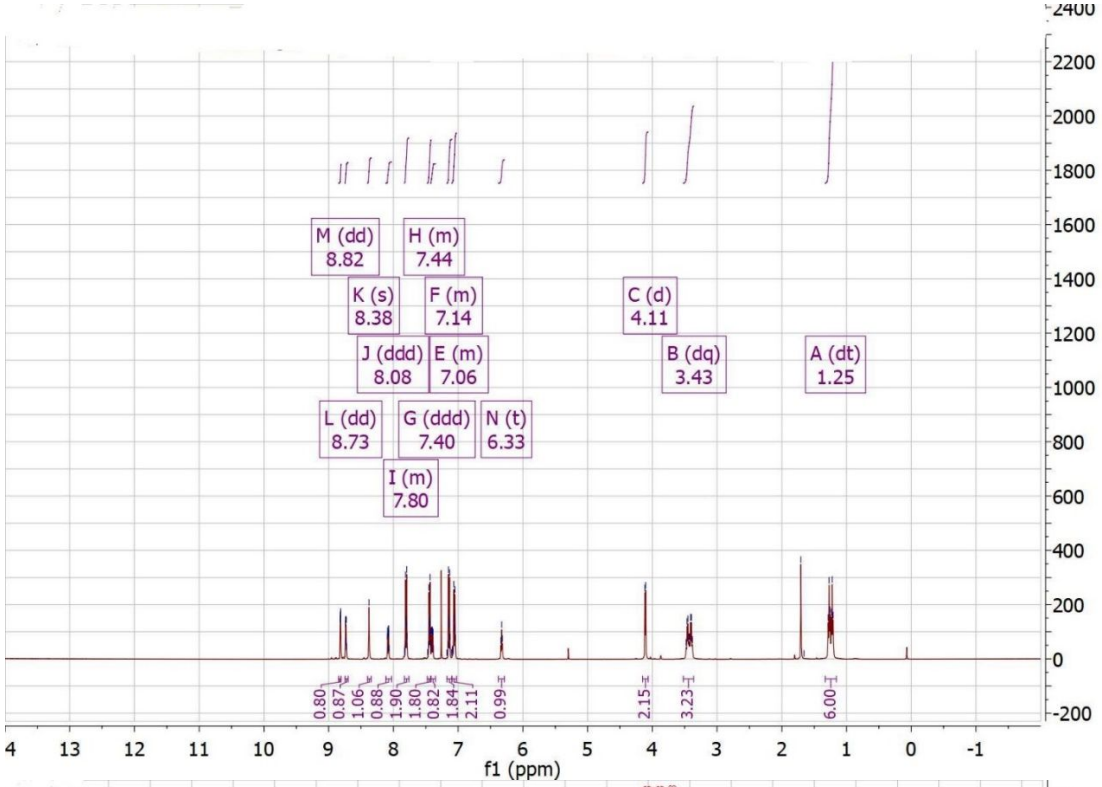


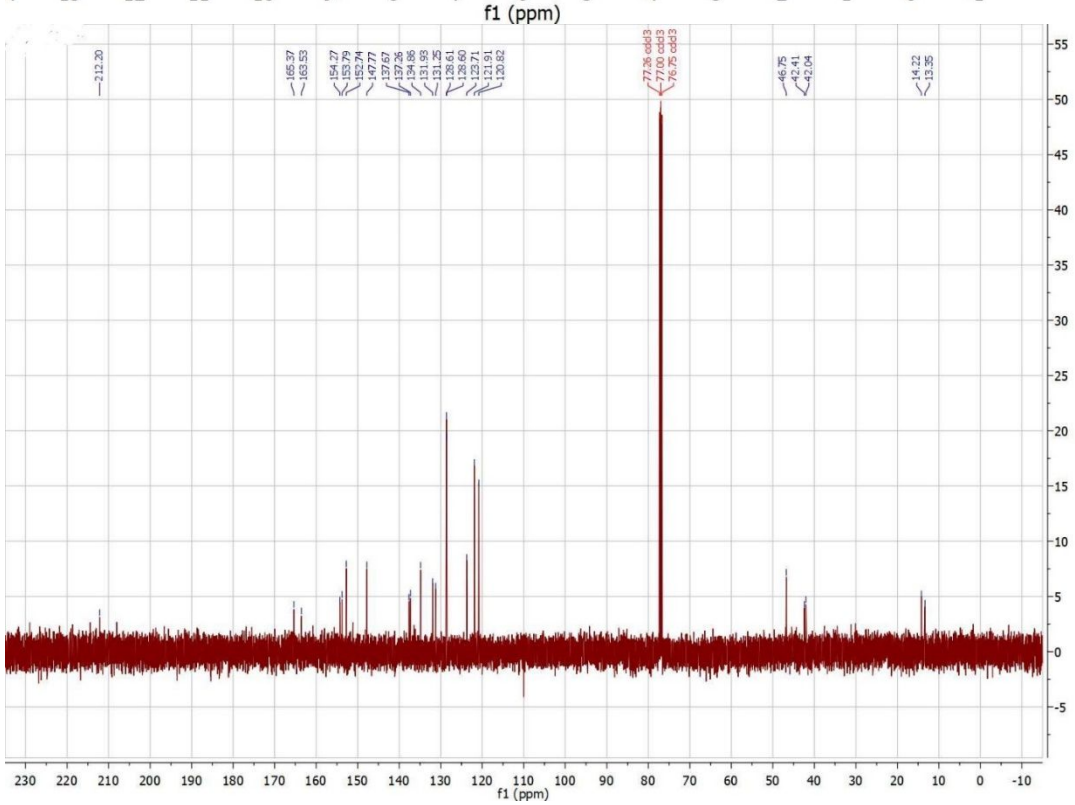


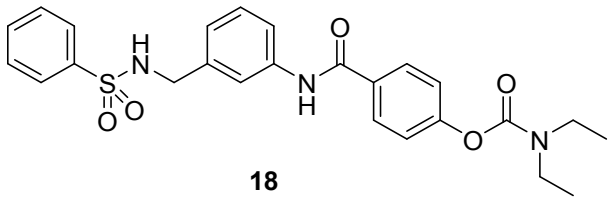
17

4-((4-((Pyridine-3-sulfonamido)methyl)phenyl)carbamoyl)phenyl diethylcarbamate (17): To a solution of 4-((4-(aminomethyl)phenyl)carbamoyl)phenyl diethylcarbamate (**15c**, 0.043g, 0.13mmol) in dry ACN (5mL) were added triethylamine (0.052g, 0.77mmol, 6eq), and pyridine-3-sulfonylchloride (0.034g, 0.19mmol, 1.5eq) and the resulting mixture was allowed to stir at rt for 36h. The crude reaction mixture was then partitioned between EtOAc (25mL) and 0.25N HCl solution (10mL). The aqueous layer was re-extracted with DCM and the combined organics were washed with sat. $NaHCO_3$ solution, 50% brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 80mg of an off-white solid. The crude materials is purified on silica using 0-50% EtOAc in hexanes to produce the title compound (**17**, 12mg, 20% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (dd, J = 2.3, 0.9 Hz, 1H), 8.73 (dd, J = 4.9, 1.6 Hz, 1H), 8.38 (s, 1H), 8.08 (ddd, J = 7.9, 2.3, 1.6 Hz, 1H), 7.83 – 7.76 (m, 2H), 7.47 – 7.42 (m, 2H), 7.40 (ddd, J = 8.0, 4.9, 0.9 Hz, 1H), 7.17 – 7.10 (m, 2H), 7.10 – 7.03 (m, 2H), 6.33 (t, J = 5.9 Hz, 1H), 4.11 (d, J = 5.9 Hz, 2H), 3.43 (dq, J = 27.0, 7.1 Hz, 3H), 1.25 (dt, J = 24.7, 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.20, 165.37, 163.53, 154.27, 153.79, 152.74, 147.77, 137.67, 137.26,

134.86, 131.93, 131.25, 128.61, 128.60, 123.71, 121.91, 120.82, 46.75, 42.41, 42.04, 14.22, 13.35. HRMS calcd for $C_{24}H_{27}O_5N_4S$, 483.16967 $[M+H]^+$;found 483.16840.

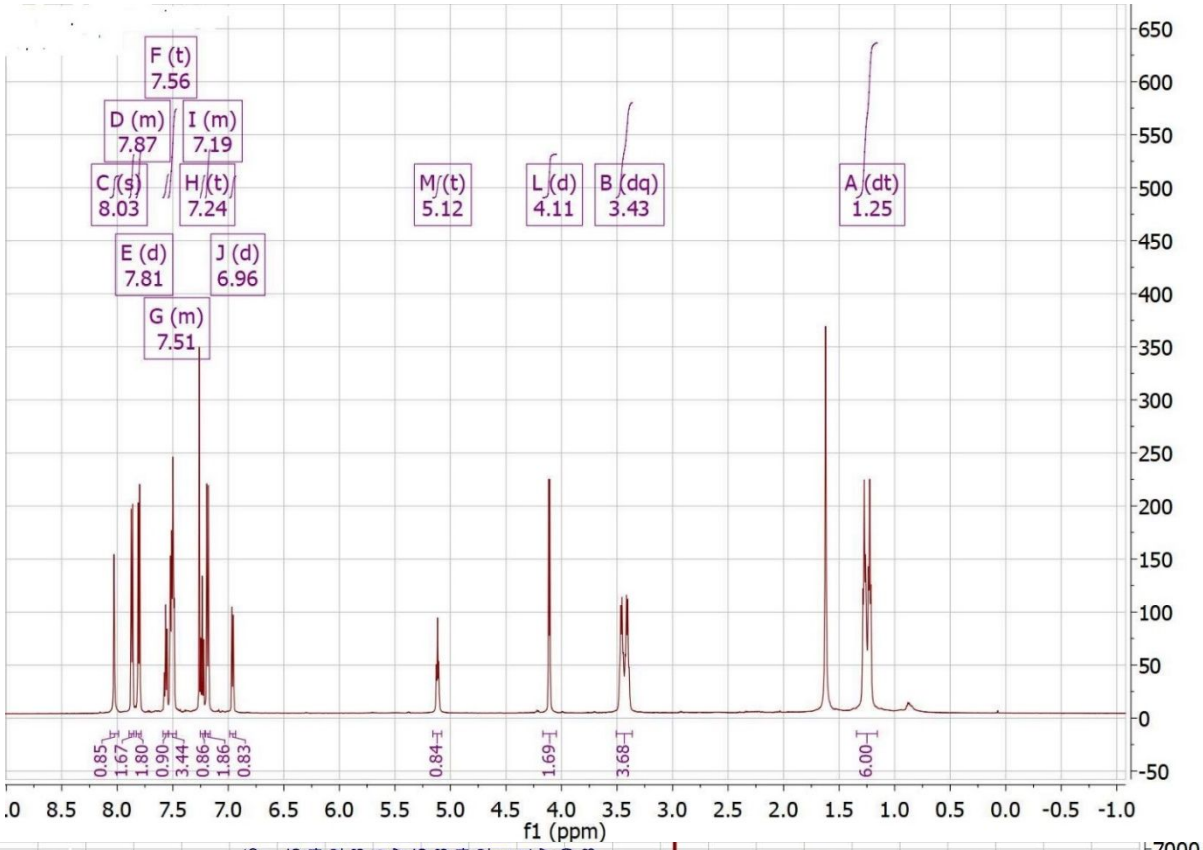


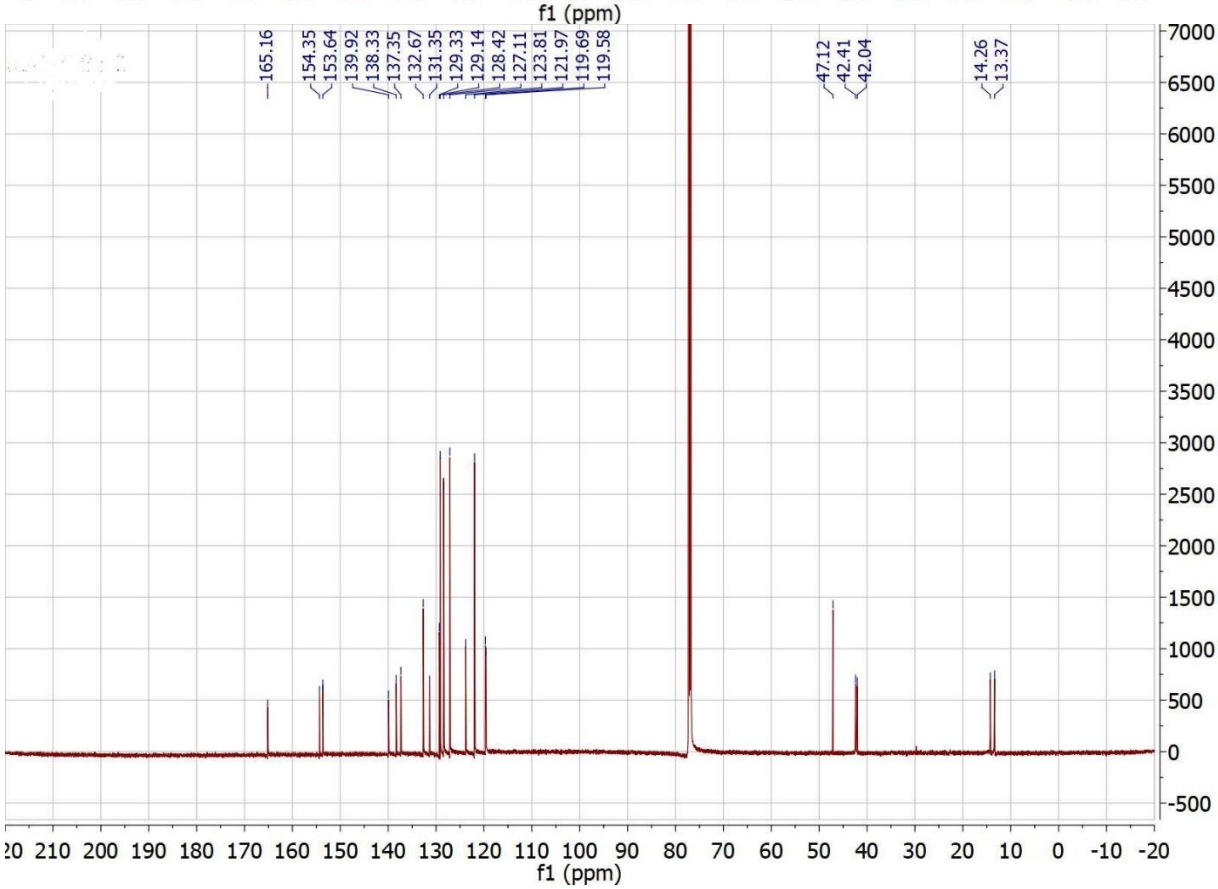




18

4-((3-(Phenylsulfonamidomethyl)phenyl)carbamoyl)phenyl diethylcarbamate (18): To a solution of 4-((3-(aminomethyl)phenyl)carbamoyl)phenyl diethylcarbamate (**15d**, 0.15g, 0.44mmol) in dry DCM (10mL) were added triethylamine (0.18g, 1.76mmol, 4eq), and benzenesulfonylchloride (0.093g, 0.53mmol, 1.2eq), and the resulting mixture was allowed to stir at room temperature for 36h. The crude reaction mixture was then partitioned between DCM (50mL) and 0.25N HCl solution (10mL). The aqueous layer was re-extracted with DCM and the combined organics were washed with sat. $NaHCO_3$ solution, 50% brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 200mg of an off-white solid. The crude material is purified on silica using 0-50% EtOAc in hexanes to produce the title compound (**18**, 150mg, 59% yield) as a white fluffy solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.89 – 7.85 (m, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.21 – 7.16 (m, 2H), 6.96 (d, *J* = 7.6 Hz, 1H), 5.12 (t, *J* = 6.3 Hz, 1H), 4.11 (d, *J* = 6.2 Hz, 2H), 3.43 (dq, *J* = 30.9, 7.2 Hz, 4H), 1.25 (dt, *J* = 29.4, 7.1 Hz, 6H). 13C NMR (151 MHz, $CDCl_3$) δ 165.16, 154.35, 153.64, 139.92, 138.33, 137.35, 132.67, 131.35, 129.33, 129.14, 128.42, 127.11, 123.81, 121.97, 119.69, 119.58, 47.12, 42.41, 42.04, 14.26, 13.37. HRMS calcd for $C_{25}H_{28}O_5N_3S$, 482.17442 $[M+H]^+$; found 482.17488.


F (t)
7.56
D (m)
7.87
I (m)
7.19
C (s)
8.03
H (t)
7.24
M (t)
5.12
L (d)
4.11
B (dq)
3.43
A (dt)
1.25
E (d)
7.81
J (d)
6.96
G (m)
7.51
0.85
1.67
1.80
0.90
3.44
0.86
1.86
0.83
0.84
1.69
3.68
6.00
f1 (ppm)


165.16
154.35
153.64
139.92
138.33
137.35
132.67
131.35
129.33
129.14
128.42
127.11
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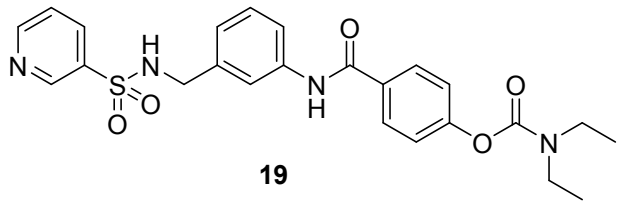
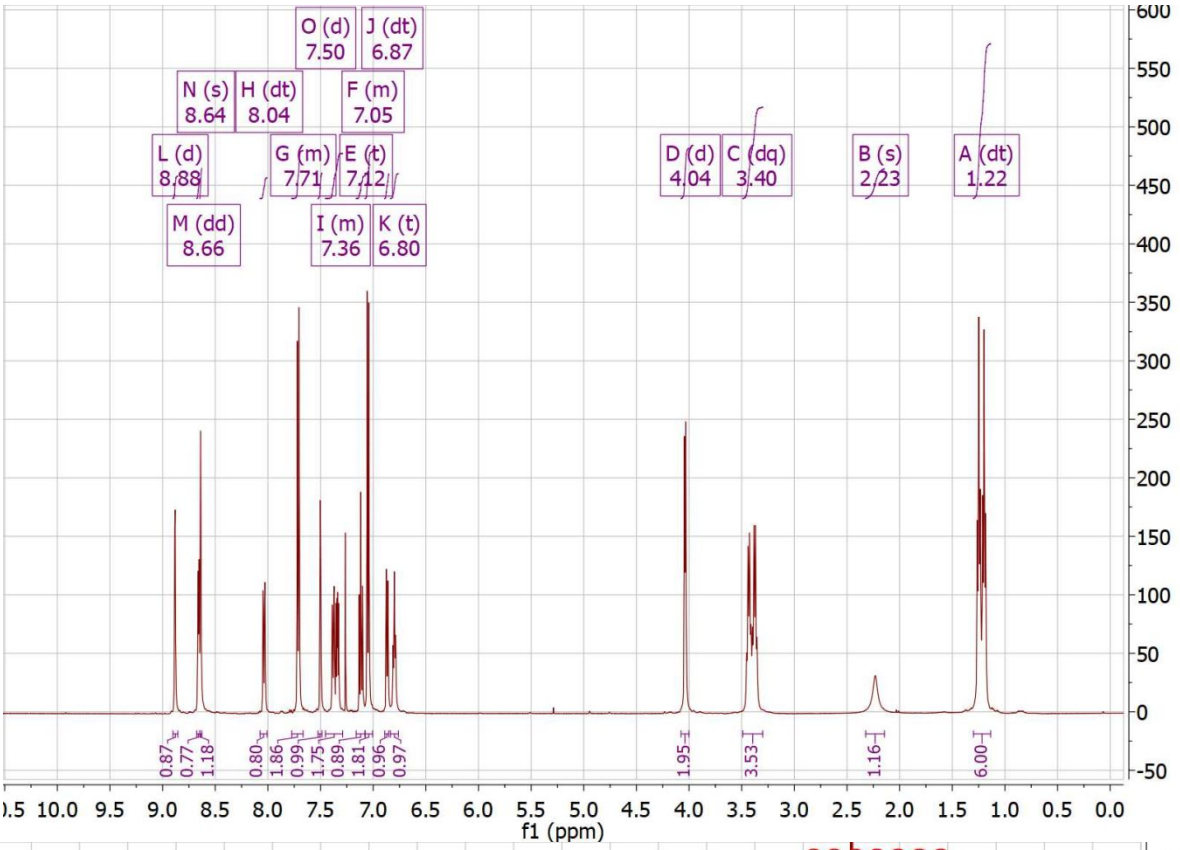
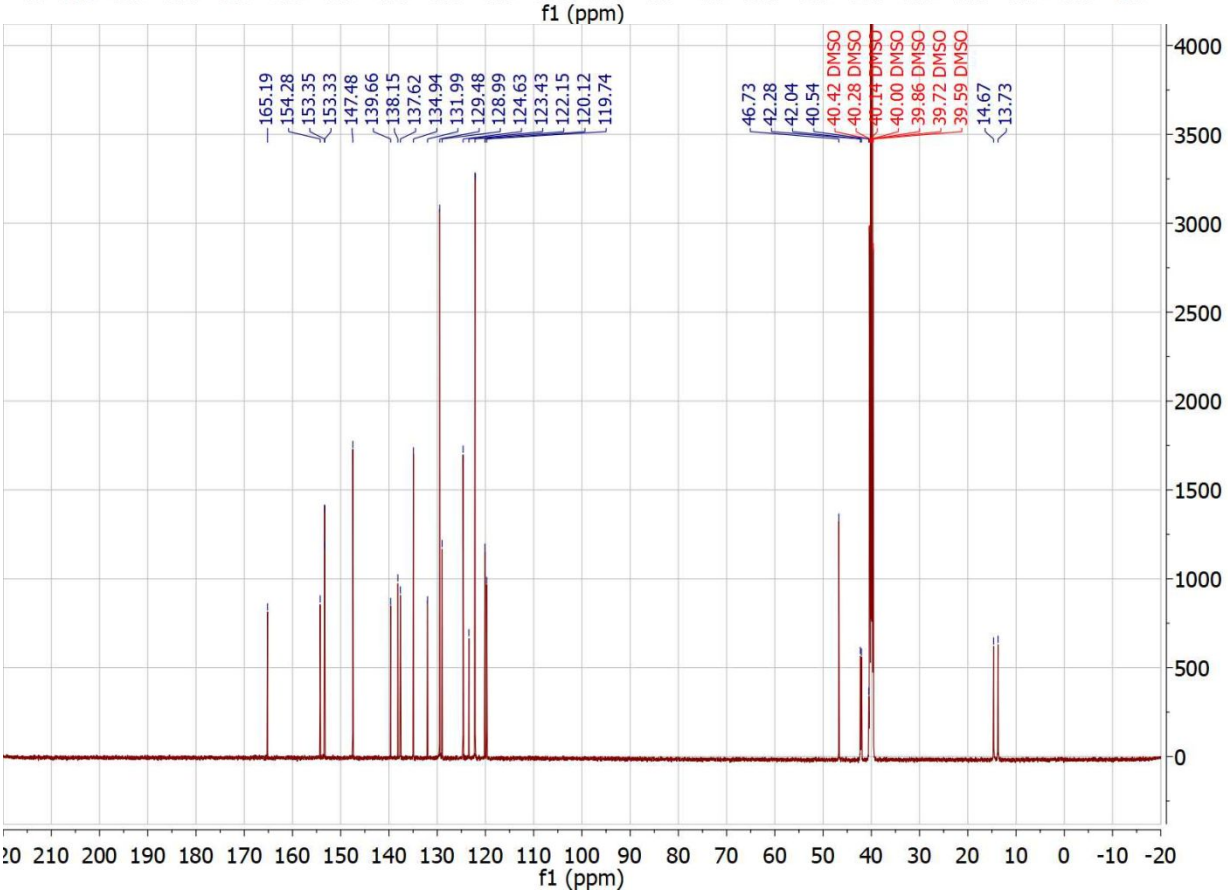
119.58
47.12
42.41
42.04
14.26
13.37
f1 (ppm)



19

4-((3-((Pyridine-3-sulfonamido)methyl)phenyl)carbamoyl)phenyl diethylcarbamate (19): To a solution of 4-((3-(Aminomethyl)phenyl)carbamoyl)phenyl diethylcarbamate (**15d**, 0.15g, 0.44mmol) in dry DCM were added triethylamine (0.18g, 1.76mmol, 4eq), and pyridine-3-sulfonylchloride (0.094g, 0.53mmol, 1.2eq) and the resulting mixture was allowed to stir at rt for 36h. The crude reaction mixture was then partitioned between DCM (50mL) and 0.25N HCl solution (10mL). The aqueous layer was re-extracted with DCM and the combined organics were washed with sat. $NaHCO_3$ solution, 50% brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 200mg of an off-white solid. Purify on silica using 0-50% EtOAc in hexanes to produce the title compound (**19**, 128mg, 60% yield) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, *J* = 2.4 Hz, 1H), 8.66 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.64 (s, 1H), 8.04 (dt, *J* = 8.1, 1.9 Hz, 1H), 7.77 – 7.67 (m, 2H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.45 – 7.29 (m, 2H), 7.12 (t, *J* = 7.8 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.87 (dt, *J* = 7.7, 1.3 Hz, 1H), 6.80 (t, *J* = 6.1 Hz, 1H), 4.04 (d, *J* = 6.0 Hz, 2H), 3.40 (dq, *J* = 28.4, 7.1 Hz, 4H), 2.23 (s, 1H), 1.22 (dt, *J* = 25.4, 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.55, 154.12, 153.80, 152.64, 147.69, 138.38, 137.21, 136.96, 134.88, 131.27, 129.11, 128.62, 123.95, 123.75, 121.80, 120.05, 119.98, 46.97, 42.40, 42.05, 14.21, 13.35. HRMS calcd for $C_{24}H_{27}O_5N_4S$, 483.16967 $[M+H]^+$; found 483.17011.


O (d) 7.50
J (dt) 6.87
N (s) 8.64
H (dt) 8.04
F (m) 7.05
L (d) 8.88
G (m) 7.71
E (t) 7.12
D (d) 4.04
C (dq) 3.40
B (s) 2.23
A (dt) 1.22
M (dd) 8.66
I (m) 7.36
K (t) 6.80
0.87
0.77
1.18
0.80
1.86
0.99
1.75
0.89
1.81
0.96
0.97
1.95
3.53
1.16
6.00
f1 (ppm)


165.19
154.28
153.35
153.33
147.48
139.66
138.15
137.62
134.94
131.99
129.48
128.99
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123.43
122.15
120.12
119.74
46.73
42.28
42.04
40.54
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40.00 DMSO
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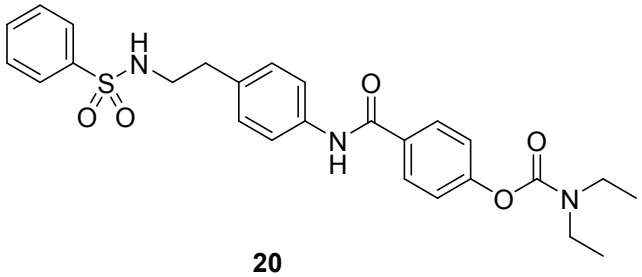
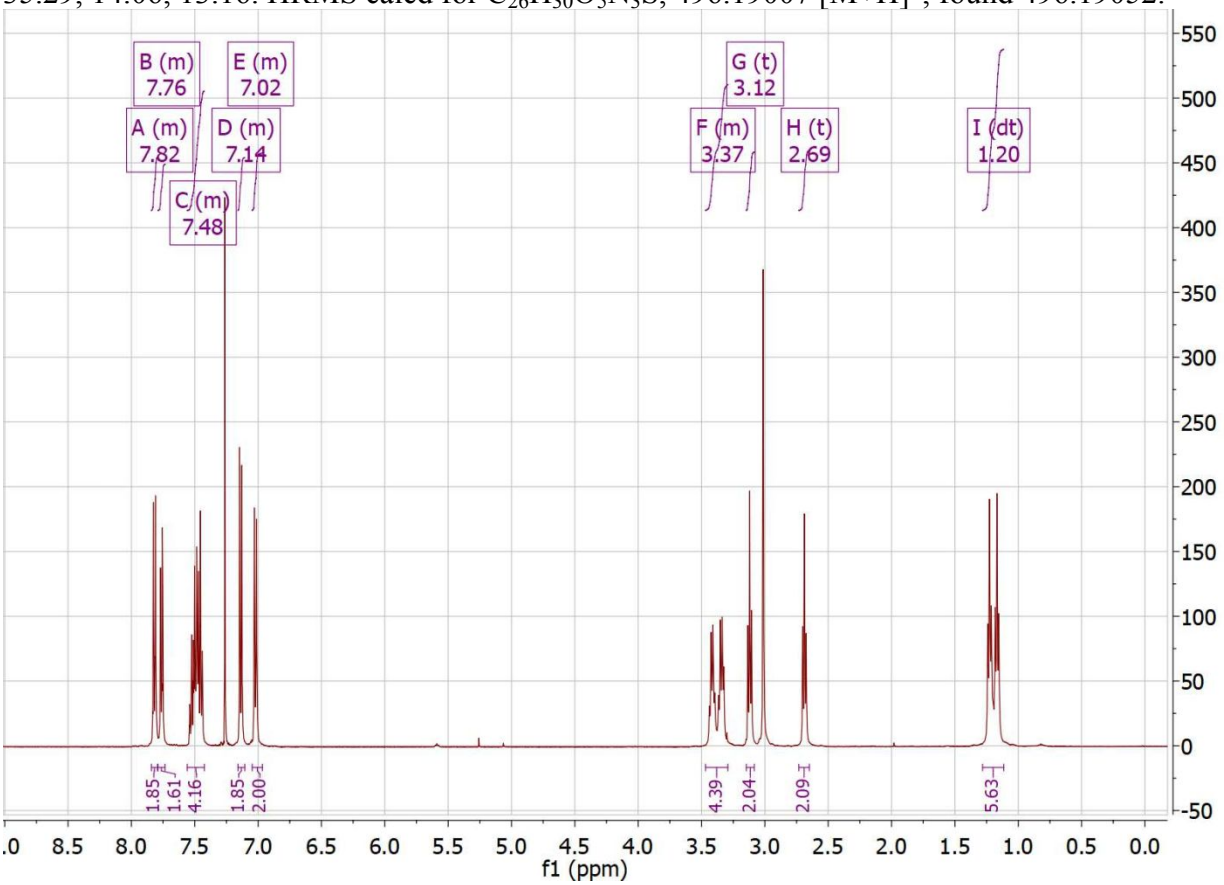
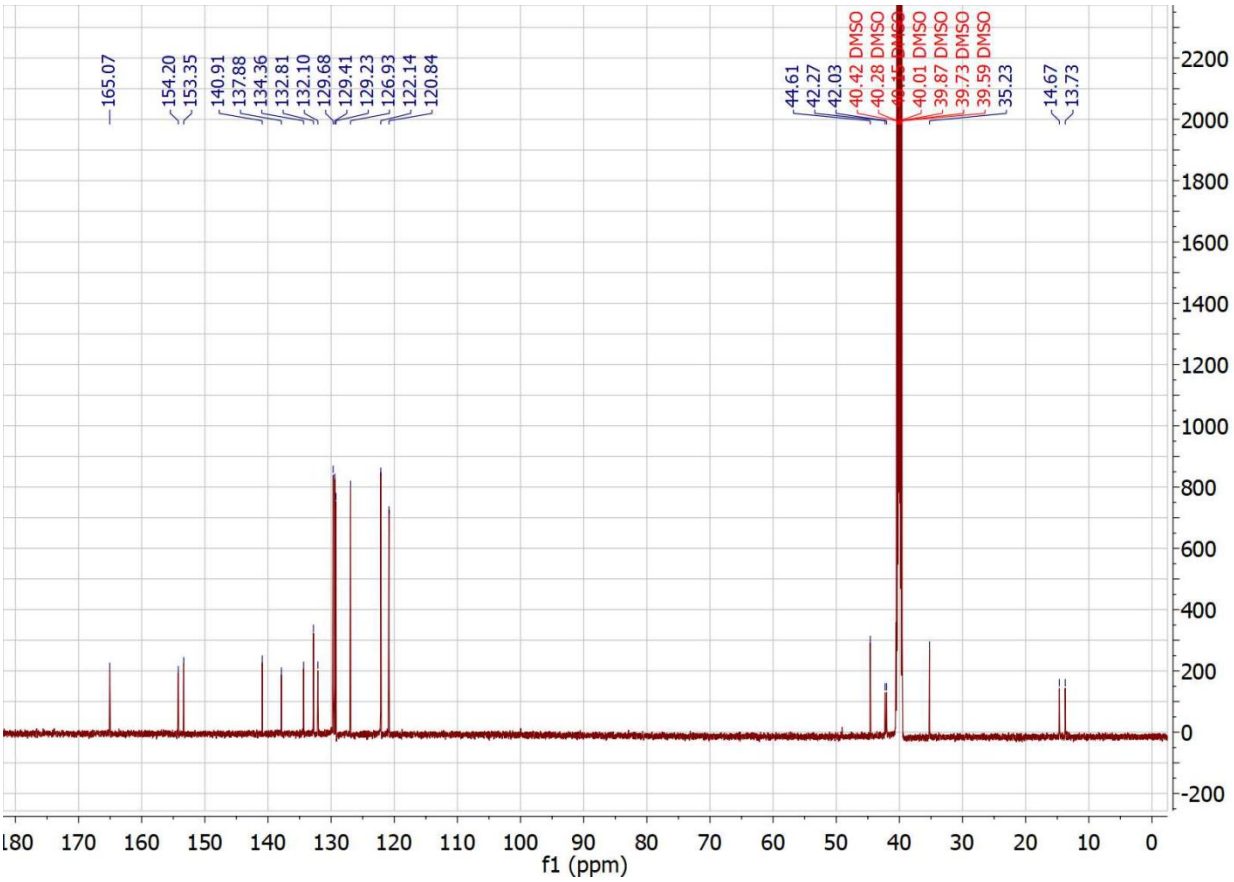
39.72 DMSO
39.59 DMSO
14.67
13.73
f1 (ppm)

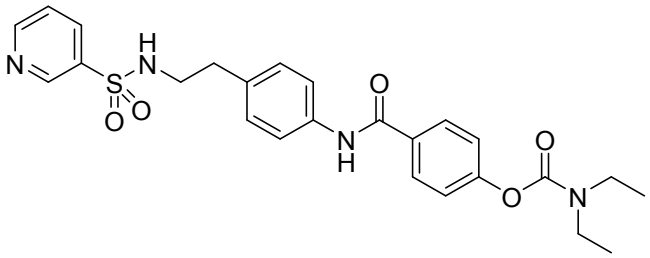


20

4-((4-(2-(Phenylsulfonamido)ethyl)phenyl)carbamoyl)phenyl diethylcarbamate (20): To a solution of [4-[[4-(2-aminoethyl)phenyl]carbamoyl]phenyl] N,N-diethylcarbamate (**15a**, 62.5mg, 0.18mmol) in DCM (0.5mL), was added a solution of benzenesulfonyl chloride (15.5mg, 0.09mmol, 0.5eq) in DCM (1mL), slowly, while being cooled at 0°C. The reaction mixture was allowed to warm to rt and stirred overnight. Upon completion by TLC/LCMS, the reaction is concentrated in vacuo and purified on silica gel column chromatography using 10% methanol in DCM with ammonia to the title compound (**20**, 39.6mg, 45.4% yield) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 2H), 7.68 (ddt, *J* = 8.5, 1.9, 0.9 Hz, 2H), 7.47 – 7.34 (m, 5H), 7.08 – 7.03 (m, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 3.40 – 3.22 (m, 4H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 1.11 (dt, *J* = 31.5, 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.03, 153.86, 134.00, 132.51, 132.03, 129.14, 129.03, 128.61, 126.84, 121.74, 120.83, 44.14, 42.37, 42.03, 35.29, 14.06, 13.16. HRMS calcd for $C_{26}H_{30}O_5N_3S$, 496.19007 $[M+H]^+$; found 496.19052.



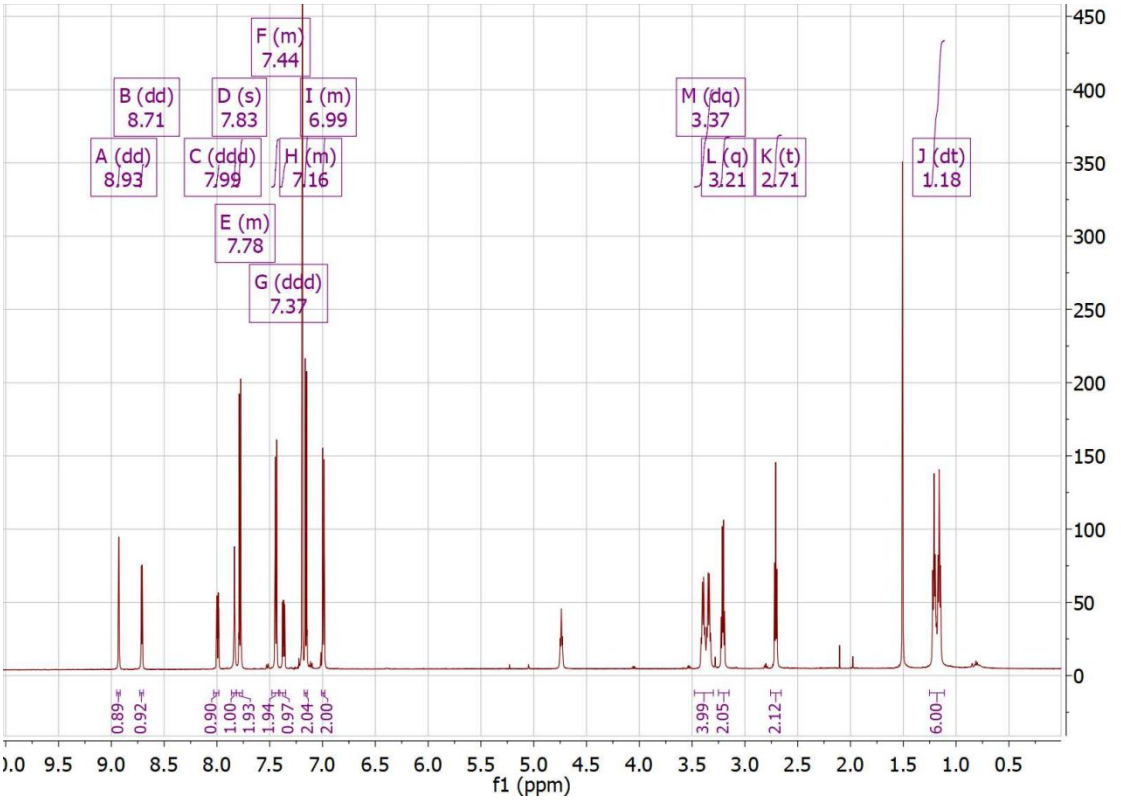


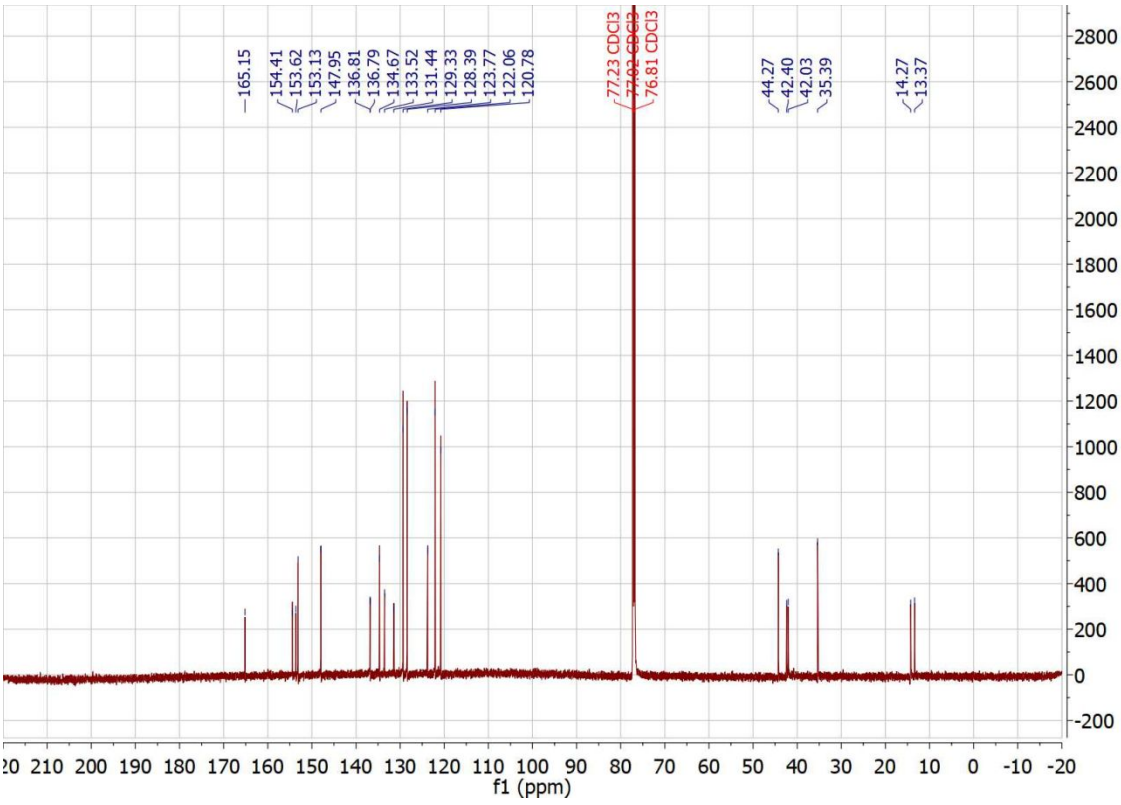


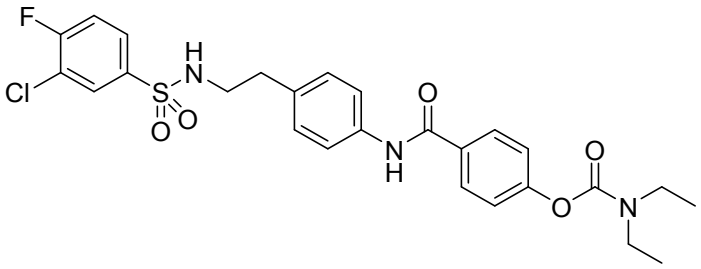
21

4-((4-(2-(Pyridine-3-sulfonamido)ethyl)phenyl)carbamoyl)phenyl diethylcarbamate (21): To a solution of [4-[[4-(2-aminoethyl)phenyl]carbamoyl]phenyl] N,N-diethylcarbamate (**15a**, 125mg, 0.35mmol) in DCM (1mL) at 0°C was added pyridine-3-sulfonylchloride (31.2mg, 0.18mmol, 0.5eq) dissolved in DCM (2mL). The mixture was allowed to warm to rt and stirred overnight until complete by TLC/LCMS. The mixture was concentrated in vacuo and the residue purified by silica gel column chromatography using 0%-80% ethyl acetate in hexanes to produce the title compound (**21**, 65.7mg, 37.6% yield) as a white foam. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.93 (dd, J = 2.4, 0.9 Hz, 1H), 8.71 (dd, J = 4.8, 1.6 Hz, 1H), 7.99 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.83 (s, 1H), 7.82 – 7.76 (m, 2H), 7.48 – 7.42 (m, 2H), 7.37 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 7.17 – 7.14 (m, 2H), 7.01 – 6.98 (m, 2H), 3.37 (dq, J = 32.0, 7.1 Hz, 4H), 3.21 (q, J = 6.5 Hz, 2H), 2.71 (t, J = 6.7 Hz, 2H), 1.18 (dt, J = 30.1, 7.1 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.15, 154.41, 153.62, 153.13, 147.95, 136.81, 136.79, 134.67, 133.52, 131.44, 129.33, 128.39, 123.77,

122.06, 120.78, 44.27, 42.40, 42.03, 35.39, 14.27, 13.37. HRMS calcd for $C_{25}H_{29}O_5N_4S$, 497.15832 $[M+H]^+$; found 497.18568.

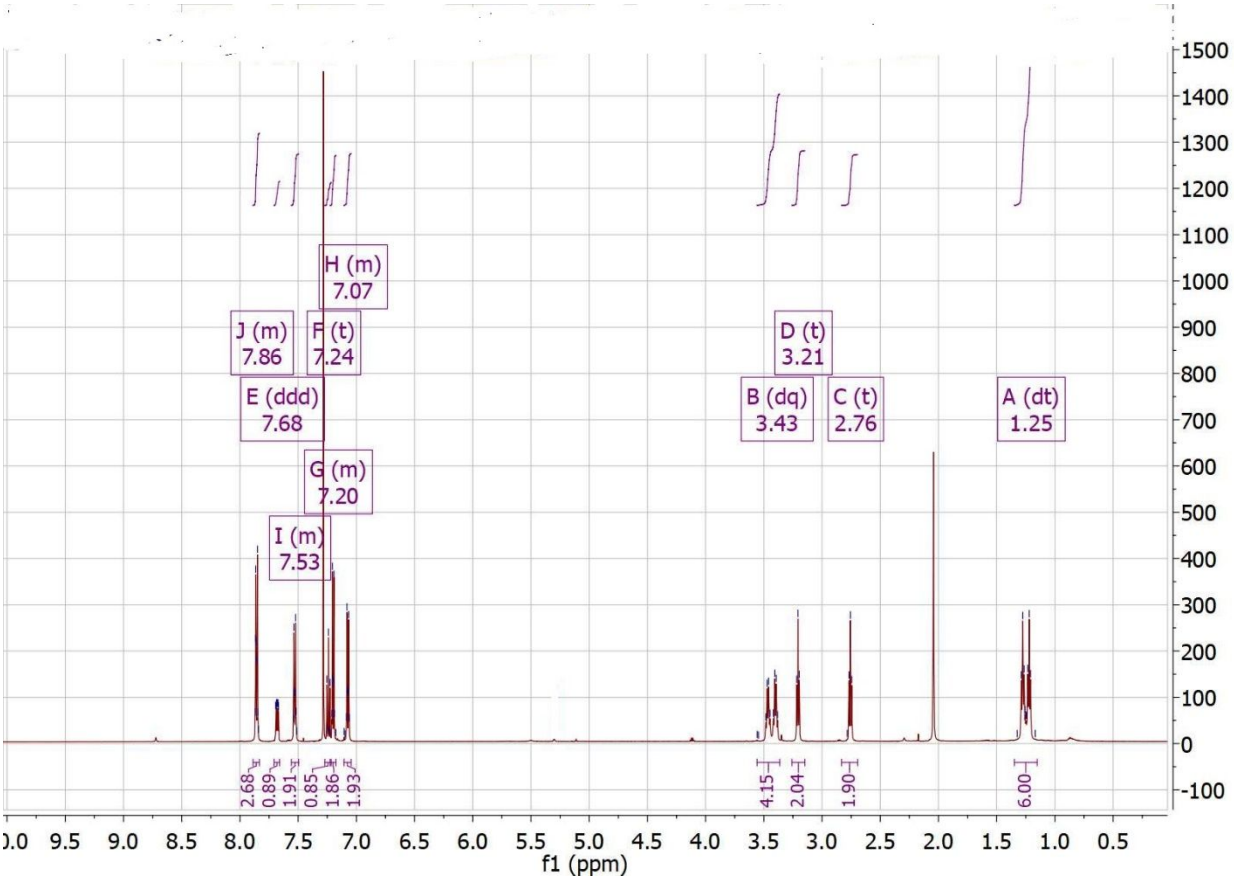


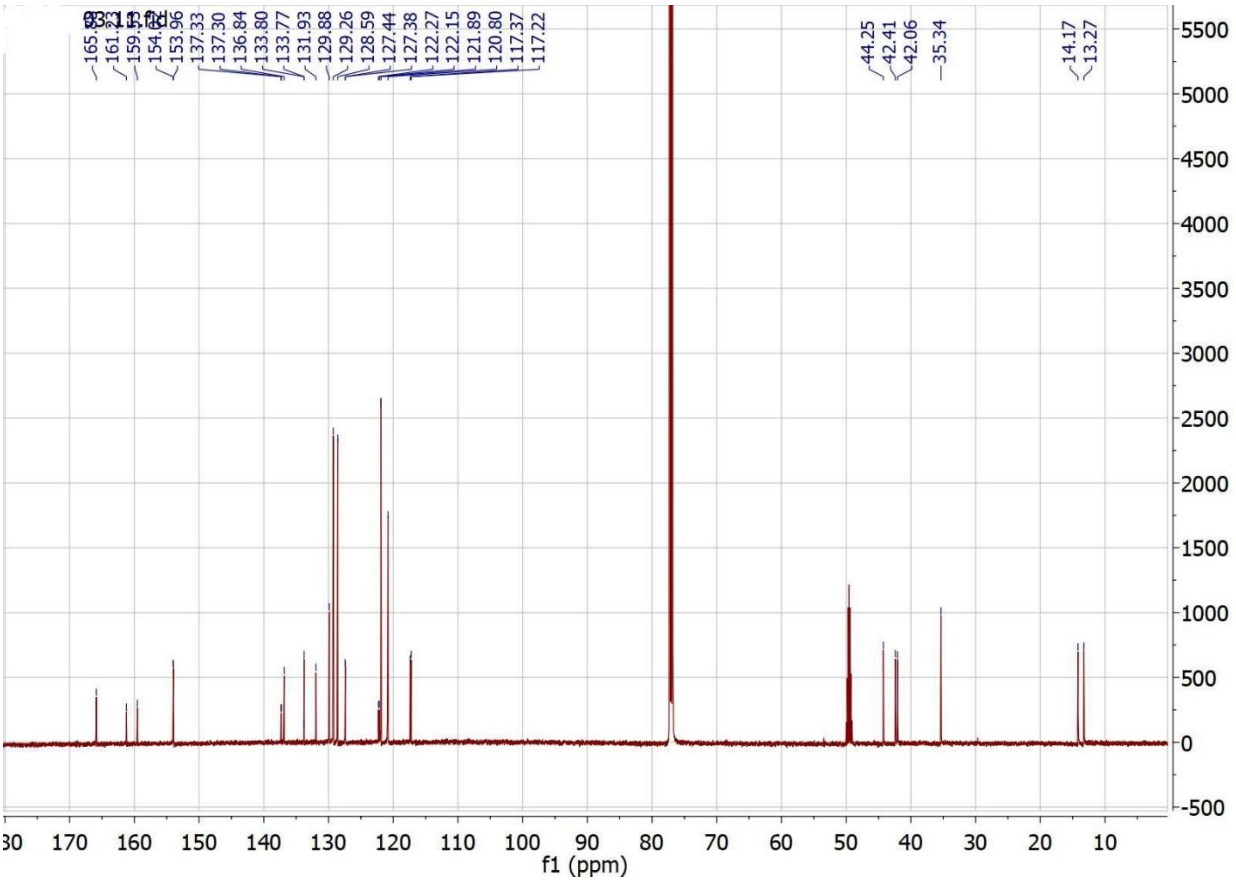


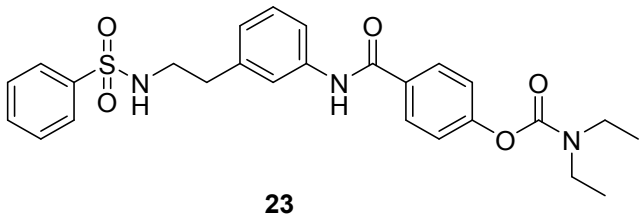


22

4-((4-(2-((3-Chloro-4-fluorophenyl)sulfonamido)ethyl)phenyl)carbamoyl)phenyl diethylcarbamate (22): To a solution of [4-[[4-(2-aminoethyl)phenyl]carbamoyl]phenyl] N,N-diethylcarbamate (**15a**, 125mg, 0.35mmol) in DCM (1mL) at 0°C was added 3-chloro-4-fluorobenzenesulfonylchloride (40.3mg, 0.18mmol, 0.5eq) in DCM (2mL). The reaction was stirred at rt until complete by TLC/LCMS. The reaction was then concentrated in vacuo and purified via silica gel column chromatography using 0-80% ethyl acetate in hexanes to produce the title compound (**22**, 82mg, 42.5% yield) as a white foam. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 3H), 7.68 (ddd, J = 8.7, 4.4, 2.3 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.24 (t, J = 8.5 Hz, 1H), 7.22 – 7.18 (m, 2H), 7.11 – 7.05 (m, 2H), 3.43 (dq, J = 39.3, 7.1 Hz, 4H), 3.21 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H), 1.25 (dt, J = 33.4, 7.1 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.88, 161.23, 159.53, 154.02, 153.96, 137.33, 137.30, 136.84, 133.80, 133.77, 131.93, 129.88, 129.26, 128.59, 127.44, 127.38, 122.27, 122.15, 121.89, 120.80, 117.37, 117.22, 44.25, 42.41, 42.06, 35.34, 14.17, 13.27. HRMS calcd for $C_{26}H_{28}O_5N_3ClFS$, 548.14167 $[M+H]^+$; found 548.14228.

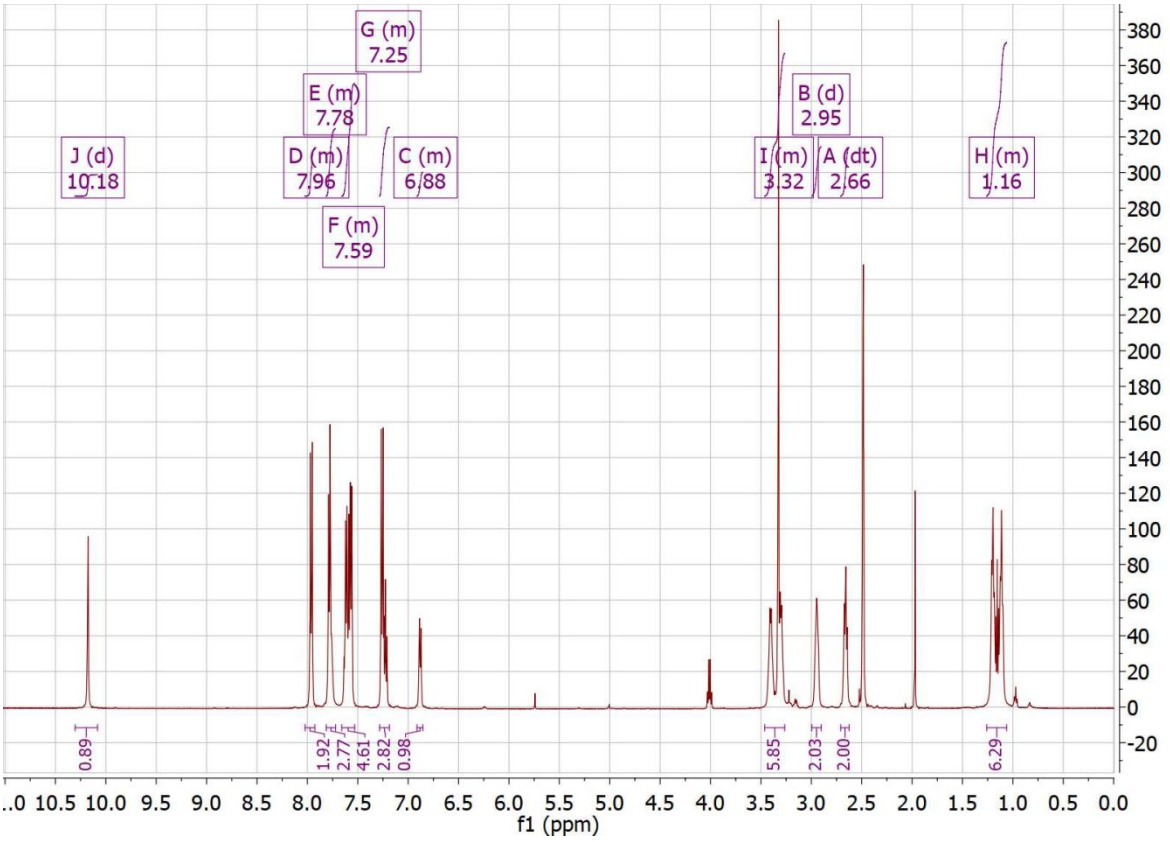






23

4-((3-(2-(Phenylsulfonamido)ethyl)phenyl)carbamoyl)phenyl diethylcarbamate (23): To a solution of [4-[[3-(2-aminoethyl)phenyl]carbamoyl]phenyl] N,N-diethylcarbamate (**15b**, 100mg, 0.28mmol) in DCM (1mL) at 0°C was added benzene sulfonyl chloride(24.85mg, 0.14mmol, 0.5eq). The reaction was stirred overnight until complete by TLC/LCMS. The solvent was removed in vacuo and the compound was purified on silica gel column chromatography using 0-20% methanol in DCM with NH_3 added produce the title compound (**23**, 65.7mg, 47.1% yield) as a white foam. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.01 – 7.92 (m, 2H), 7.82 – 7.71 (m, 3H), 7.65 – 7.52 (m, 4H), 7.31 – 7.19 (m, 3H), 6.92 – 6.85 (m, 1H), 3.47 – 3.24 (m, 6H), 2.94 (d, J = 8.4 Hz, 2H), 2.66 (dt, J = 9.2, 5.0 Hz, 2H), 1.25 – 1.05 (m, 7H). ^{13}C NMR (126 MHz, DMSO-d6) δ 165.12, 154.21, 153.32, 140.79, 139.62, 139.46, 132.82, 132.03, 129.68, 129.41, 129.04, 126.90, 124.42, 122.13, 120.93, 118.82, 44.58, 42.03, 42.00, 35.97, 14.54, 13.71. HRMS calcd for $C_{26}H_{30}O_5N_3S$, 496.19007 $[M+H]^+$; found 496.19053.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E (m)
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B (d)
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J (d)
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D (m)
7.96
C (m)
6.88
I (m)
3.32
A (dt)
2.66
H (m)
1.16
F (m)
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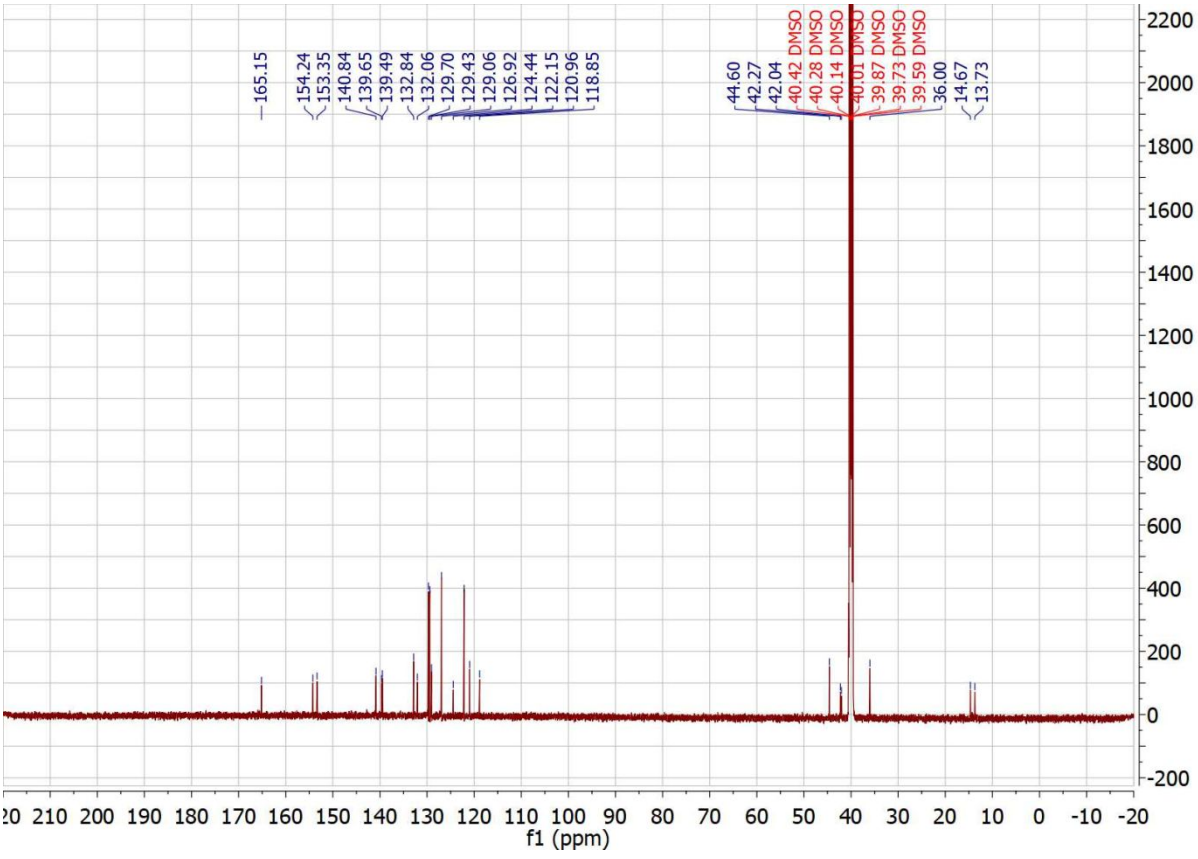
2.03
2.00
6.29
f1 (ppm)


165.15
154.24
153.35
140.84
139.65
139.49
132.84
132.06
129.70
129.43
129.06
126.92
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122.15
120.96
118.85
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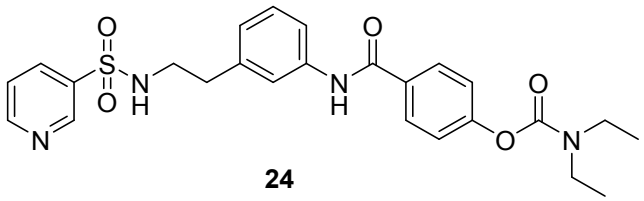
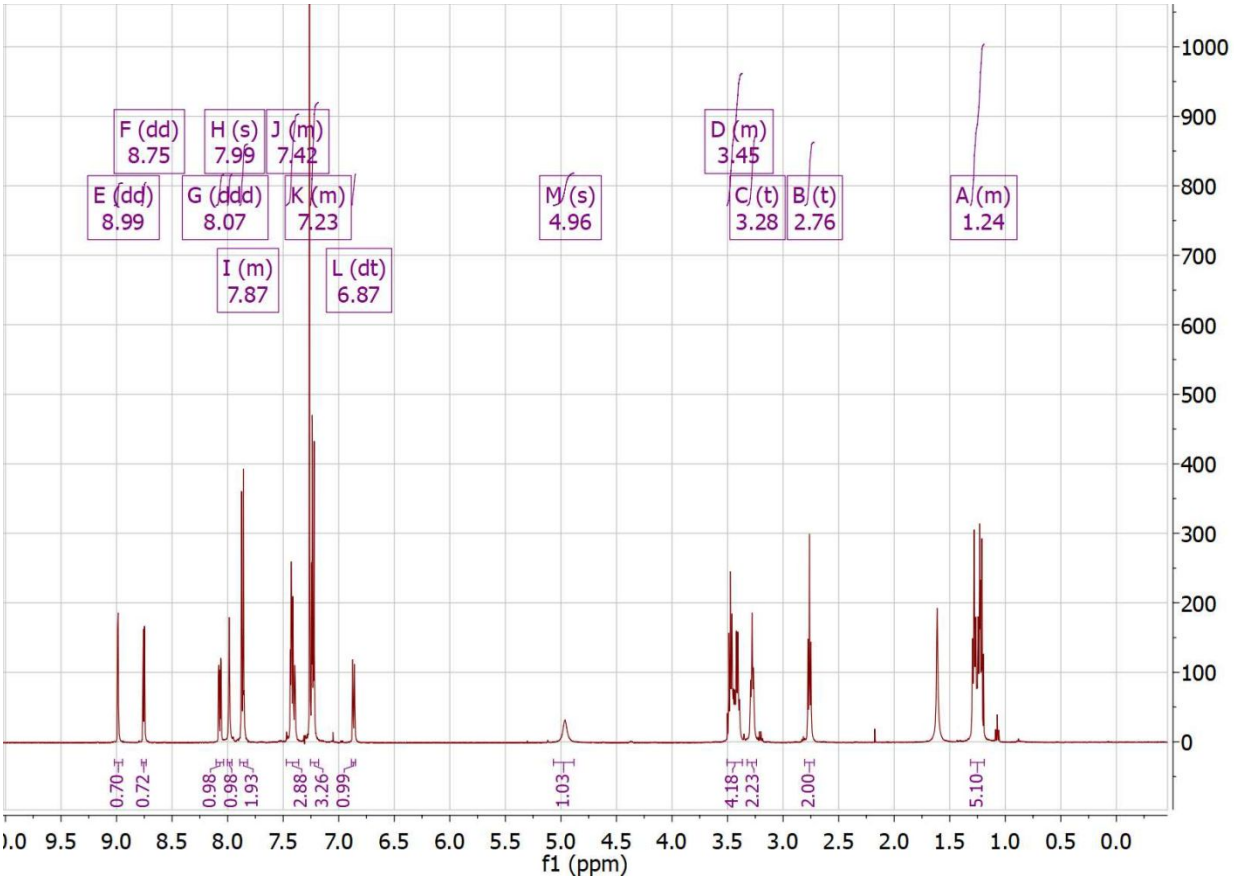
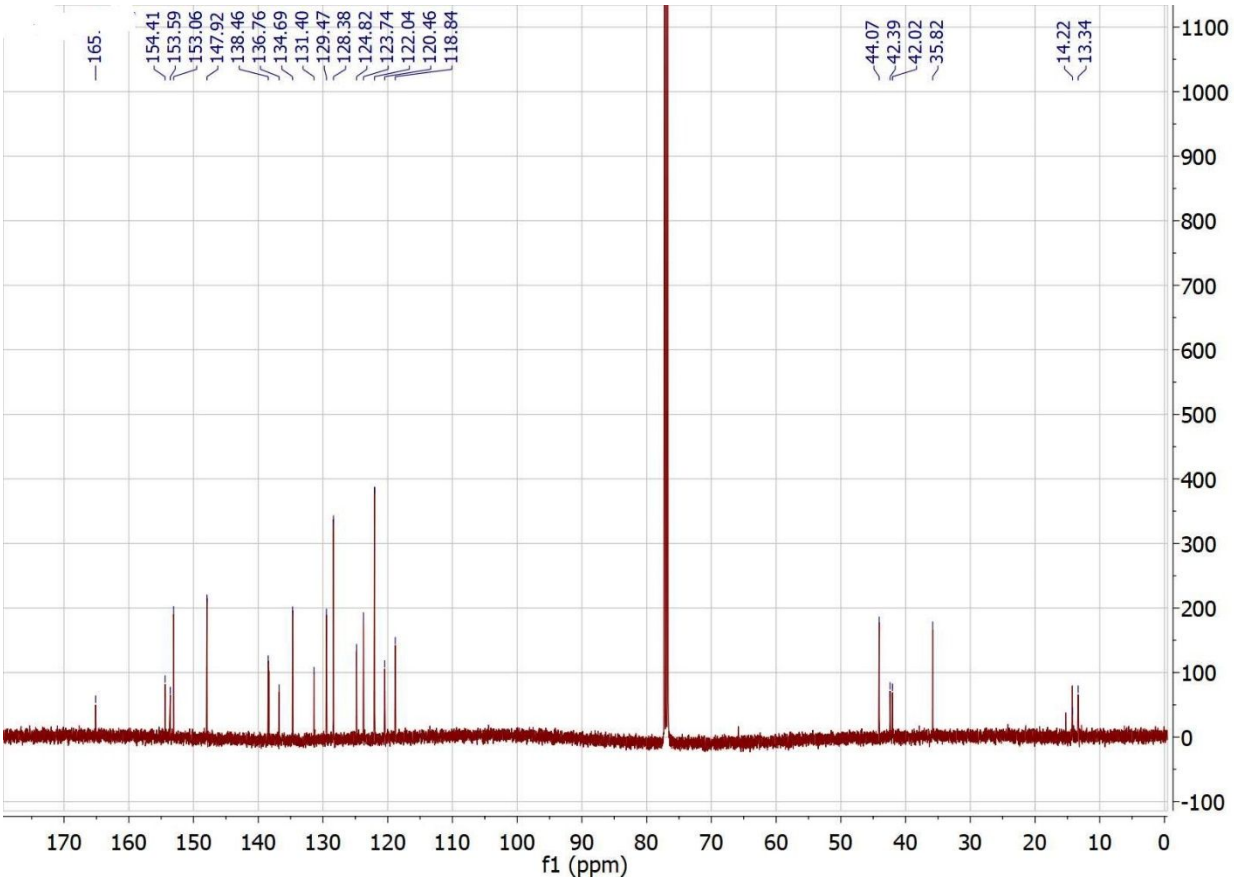
39.59 DMSO
36.00
14.67
13.73
f1 (ppm)

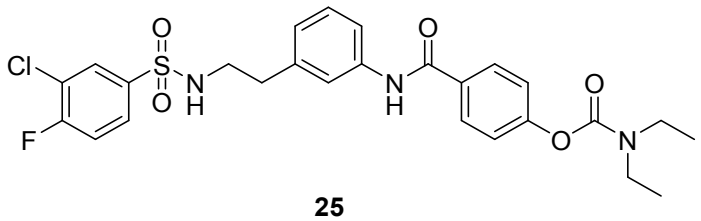


24

4-((3-(2-(Pyridine-3-sulfonamido)ethyl)phenyl)carbamoyl)phenyl diethylcarbamate (24): To a solution of [4-[[3-(2-aminoethyl)phenyl]carbamoyl]phenyl] N,N-diethylcarbamate (**15b**, 100mg, 0.28mmol) in DCM (1mL) at 0°C was added pyridine-3-sulfonylchloride (24.9mg, 0.14mmol, 0.5eq). The reaction was stirred at room temperature until complete by TLC/LCMS. The solvent was removed in vacuo and the residue purified via silica gel column chromatography using 0-20% methanol in DCM with NH_3 to produce the title compound (**23**, 26.6mg, 19.0% yield) as a white foam.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (dd, J = 2.3, 0.9 Hz, 1H), 8.75 (dd, J = 4.8, 1.6 Hz, 1H), 8.07 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.99 (s, 1H), 7.91 – 7.82 (m, 2H), 7.46 – 7.38 (m, 3H), 7.25 – 7.21 (m, 2H), 6.87 (dt, J = 7.8, 1.2 Hz, 1H), 3.51 – 3.38 (m, 4H), 3.28 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H), 1.33 – 1.20 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.12, 154.41, 153.59, 153.06, 147.92, 138.46, 138.36, 136.76, 134.69, 131.40, 129.47, 128.38, 124.82, 123.74, 122.04, 120.46, 118.84, 44.07, 42.39, 42.02, 35.82, 14.22, 13.34. HRMS calcd for $C_{25}H_{29}O_5N_4S$, 497.18532 $[M+H]^+$; found 497.18584.

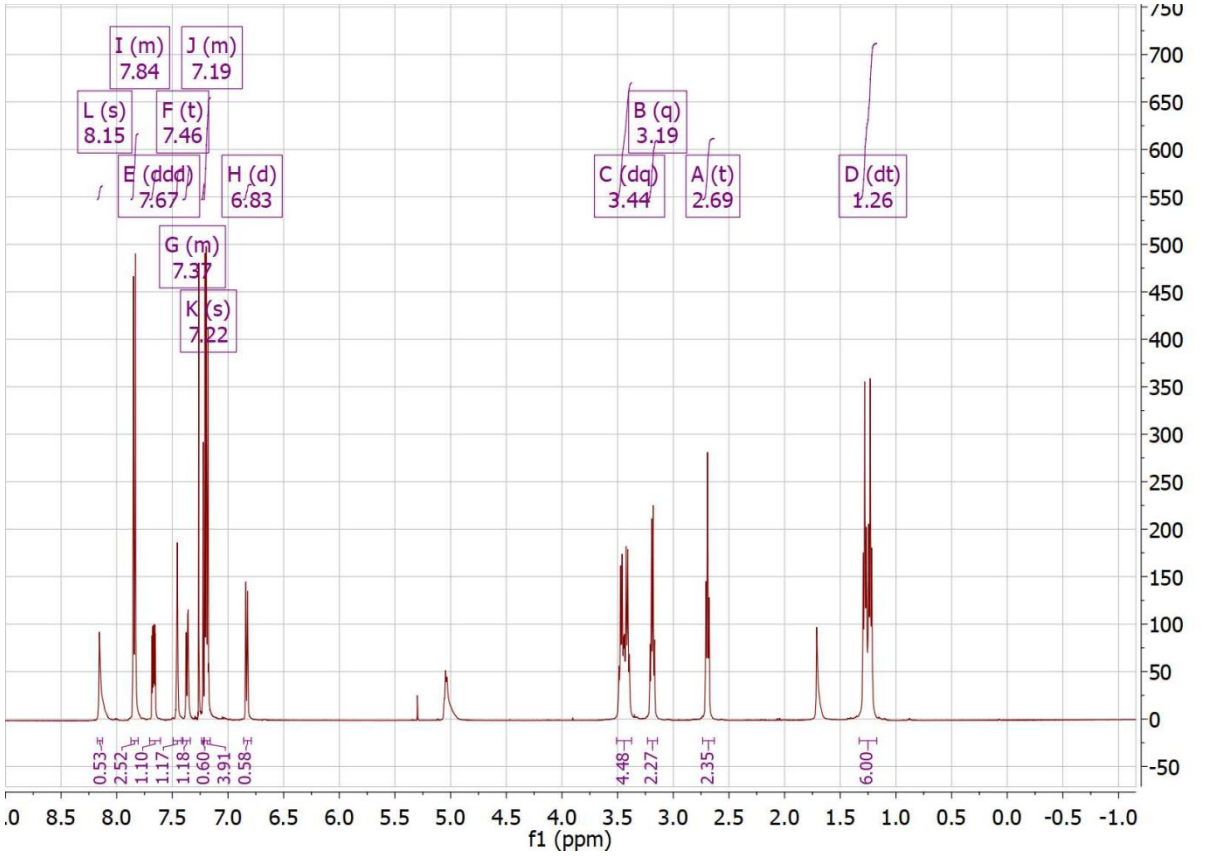






25

4-((3-(2-((3-Chloro-4-fluorophenyl)sulfonamido)ethyl)phenyl)carbamoyl)phenyl diethylcarbamate (25): To a solution of [4-[[3-(2-aminoethyl)phenyl]carbamoyl]phenyl] N,N-diethylcarbamate (**15b**, 100mg, 0.28mmol) in DCM (1mL) at 0°C was added 3-chloro-4-fluorobenzenesulfonylchloride (24.85mg, 0.14mmol, 0.5eq) in DCM (1mL). The reaction stirred overnight until complete by TLC/LCMS. The solvent was removed in vacuo and the compound was purified on silica gel column chromatography using 0-20% methanol in DCM with NH_3 added to produce the title compound (**25**, 65.7mg, 47.1% yield) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.87 – 7.82 (m, 3H), 7.67 (ddd, *J* = 8.7, 4.4, 2.3 Hz, 1H), 7.46 (s, 1H), 7.40 – 7.34 (m, 1H), 7.22 (s, 1H), 7.21 – 7.16 (m, 4H), 6.83 (dt, *J* = 7.6, 1.3 Hz, 1H), 3.44 (dq, *J* = 25.5, 7.1 Hz, 4H), 3.19 (q, *J* = 6.6 Hz, 2H), 2.69 (t, *J* = 6.9 Hz, 3H), 1.26 (dt, *J* = 24.8, 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.19, 161.42, 159.38, 154.33, 153.69, 138.55, 138.35, 137.15, 131.40, 129.89, 129.30, 128.47, 127.52, 127.46, 124.76, 122.31, 121.99, 120.55, 118.77, 117.37, 117.19, 44.13, 42.40, 42.04, 35.73, 14.23, 13.35. HRMS calcd for $C_{26}H_{28}O_5N_3ClFS$, $[M+H]^+$; 548.14167 found 548.14130.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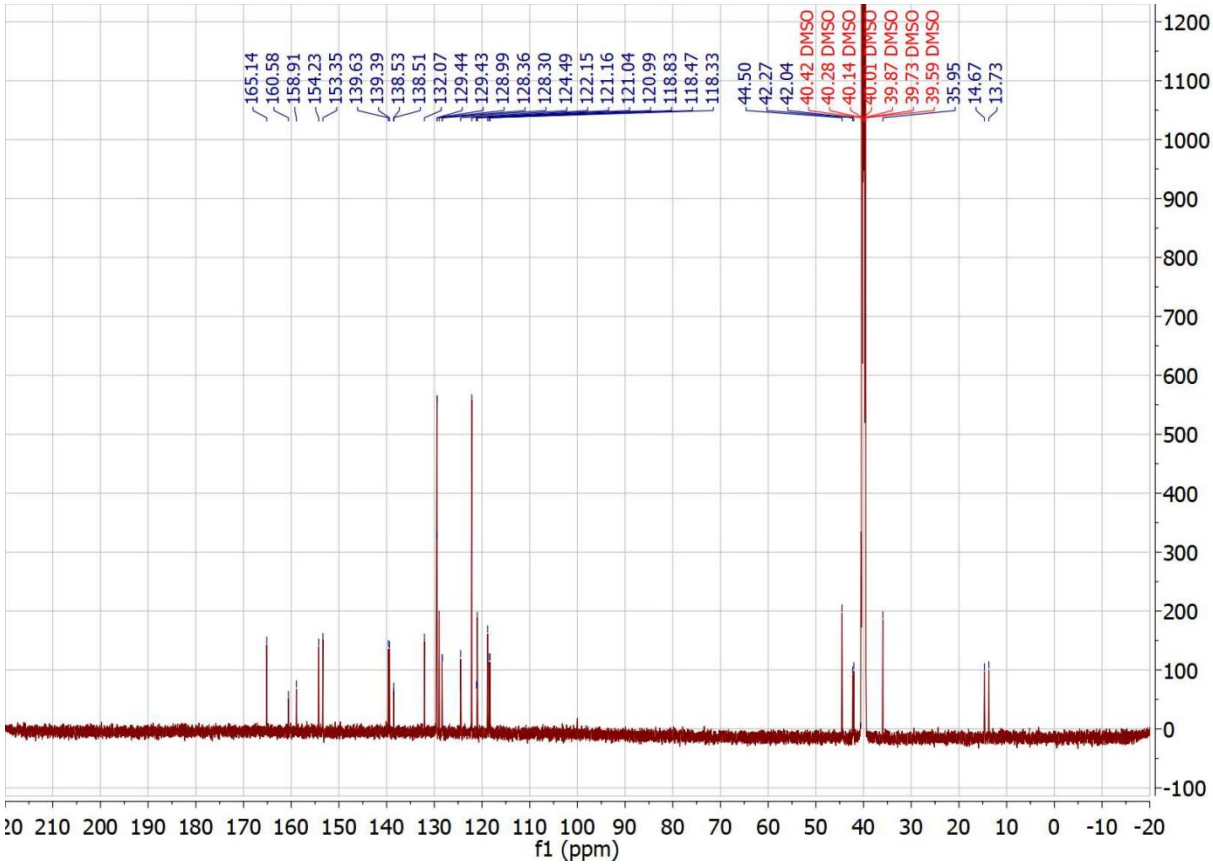
7.84
J (m)
7.19
L (s)
8.15
F (t)
7.46
E (ddd)
7.67
H (d)
6.83
G (m)
7.37
K (s)
7.22
B (q)
3.19
C (dq)
3.44
A (t)
2.69
D (dt)
1.26
0.53
2.52
1.10
1.17
1.18
0.60
3.91
0.58
4.48
2.27
2.35
6.00
f1 (ppm)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154.23
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139.63
139.39
138.53
138.51
132.07
129.44
129.43
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128.36
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118.33
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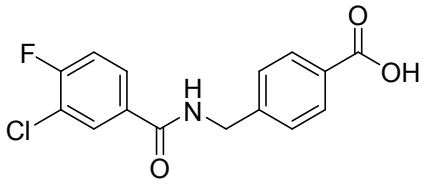
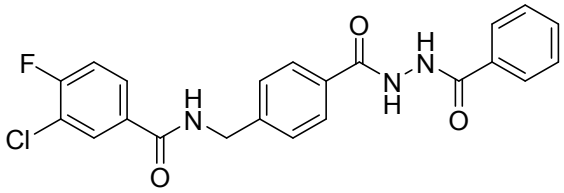
39.59 DMSO
35.95
14.67
13.73
f1 (ppm)

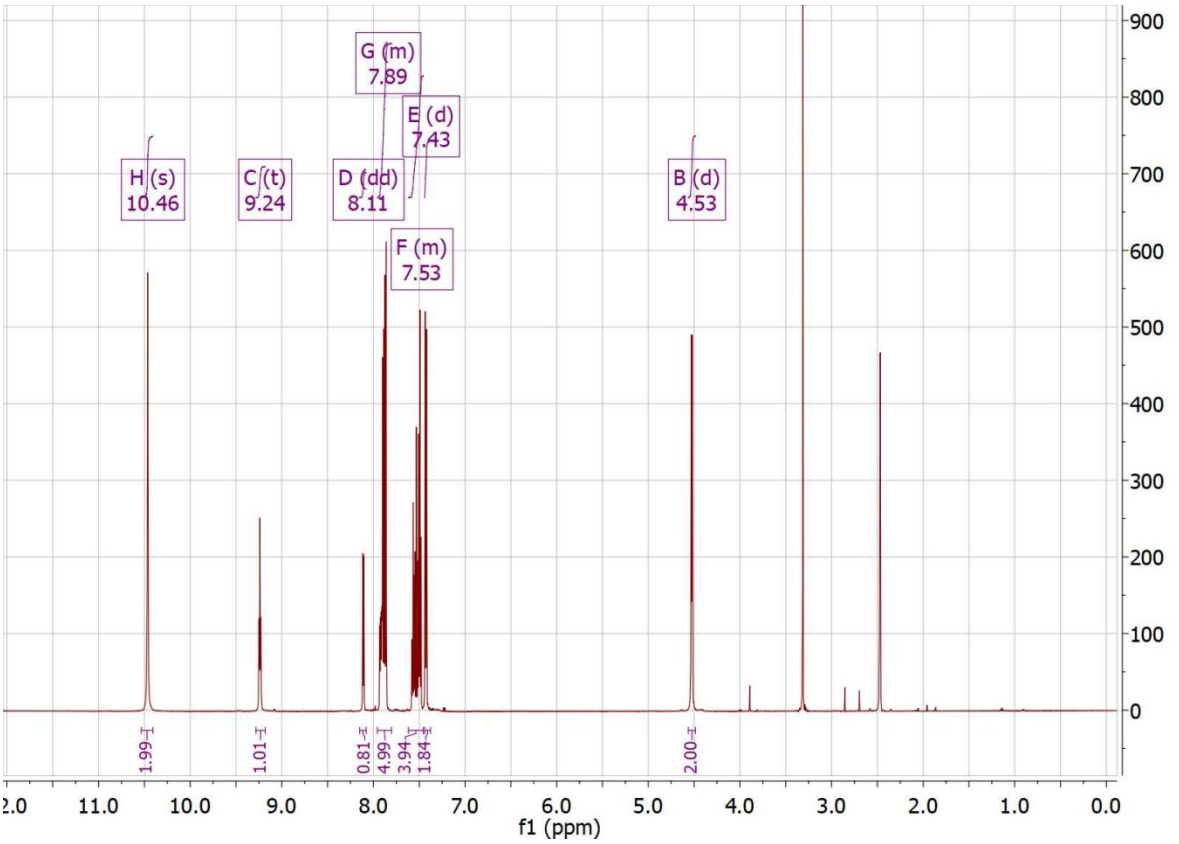


4-((3-Chloro-4-fluorobenzamido)methyl)benzoic acid: 4-(Aminomethyl)benzoyl methyl ester hydrochloride (1.27g, 7.6mmol) was dissolved in CH_2Cl_2 (25mL) at room temperature. Trimethylamine (3.19g, 31.5 mmol, 4.1eq) and 3-chloro-4-fluorobenzoyl chloride (1.2 g, 6.3 mmol, 0.8eq) were added and the mixture was stirred overnight. The reaction was quenched with water and the organic layer separated. The aqueous layer was extracted with DCM and the combined organic layers were dried and concentrated, and the crude material was used in the next step without purification. The methyl ester was dissolved in MeOH (31 mL) and a 1M KOH (31.5 mL) was added. The reaction mixture was stirred overnight going from cloudy to clear. The reaction mixture was neutralized with 6M HCl solution and the product precipitated out of the solution. The precipitate was filtered, and dried and used in the next step without further purification.



26

N-(4-(2-Benzoylhydrazine-1-carbonyl)benzyl)-3-chloro-4-fluorobenzamide (26): 4-((3-Chloro-4-fluorobenzamido)methyl)benzoic acid (0.21g, 0.7 mmol), benzhydrazide (0.12g, 0.8mmol, 1.14eq), EDC (0.15g,1.03mmol, 1.5 eq), HOBt (0.13g, 0.9mmol, 1.3eq) and diisopropylethylamine (0.36g , 2.8mmol, 4eq) were dissolved in DMF (2.8mL) at room temperature and stirred overnight. The reaction was quenched with water and a precipitate formed. The solid was collected by vacuum filtration, washed with water and dried to produce the title compound (**26**, 0.23g, 77% yield) as a white foam. ^{1}H NMR (600 MHz, DMSO-d6) δ 10.46 (s, 2H), 9.24 (t, *J* = 6.0 Hz, 1H), 8.11 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.96 – 7.80 (m, 5H), 7.62 – 7.46 (m, 4H), 7.43 (d, *J* = 8.0 Hz, 2H), 4.53 (d, *J* = 5.8 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d6) δ 166.75, 166.25, 166.09, 145.63, 144.18, 134.63, 133.02, 132.29, 131.78, 131.51, 128.96, 128.81, 127.98, 127.87, 127.71, 127.56, 119.30, 42.87. HRMS calcd for $C_{22}H_{18}ClFN_3O_3$, 426.10152 $[M+H]^+$; found 426.10192.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E (d)
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10.46
C (t)
9.24
D (dd)
8.11
B (d)
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F (m)
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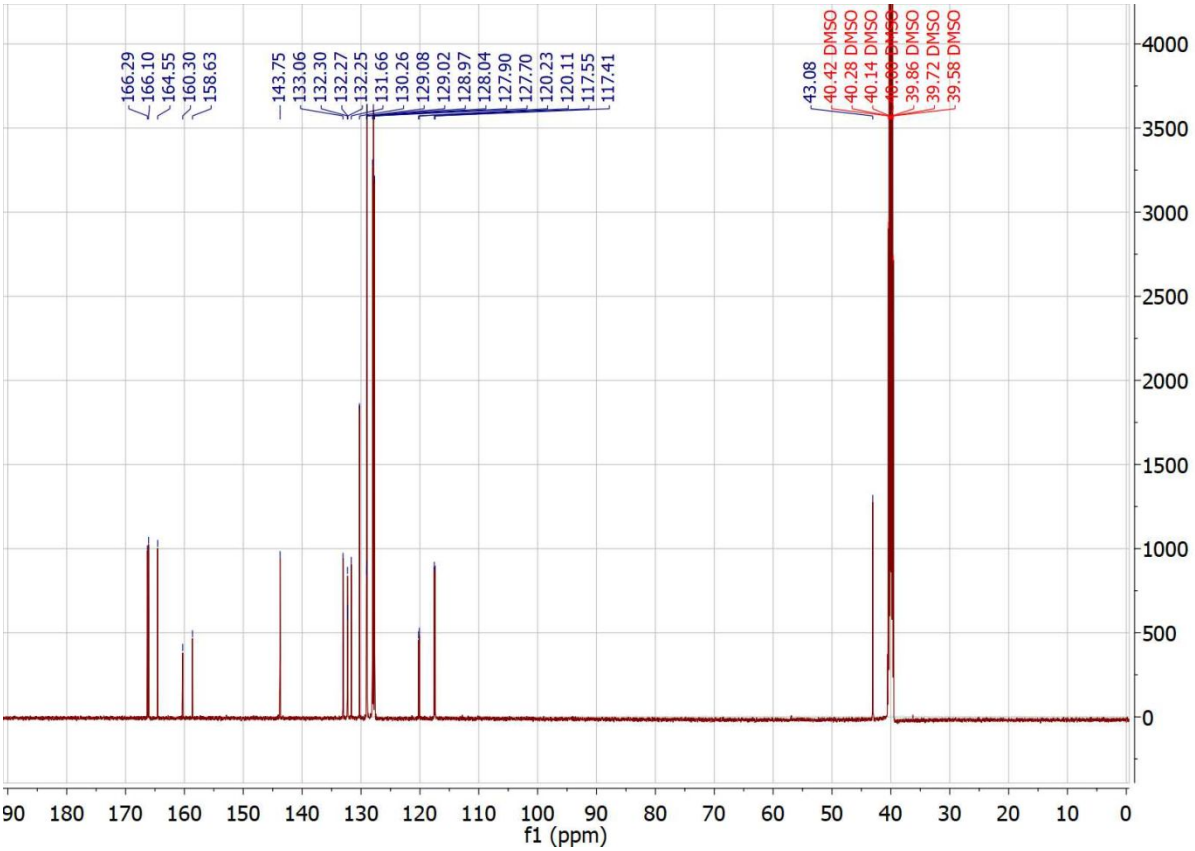
1.01
0.81
4.99
3.94
1.84
2.00
f1 (ppm)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132.30
132.27
132.25
131.66
130.26
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129.02
128.97
128.04
127.90
127.70
120.23
120.11
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43.08
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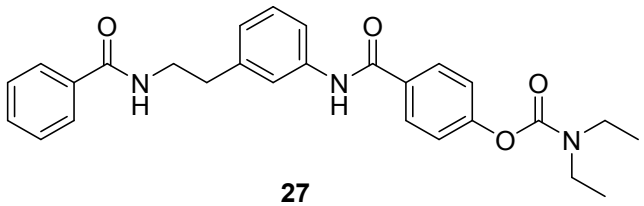
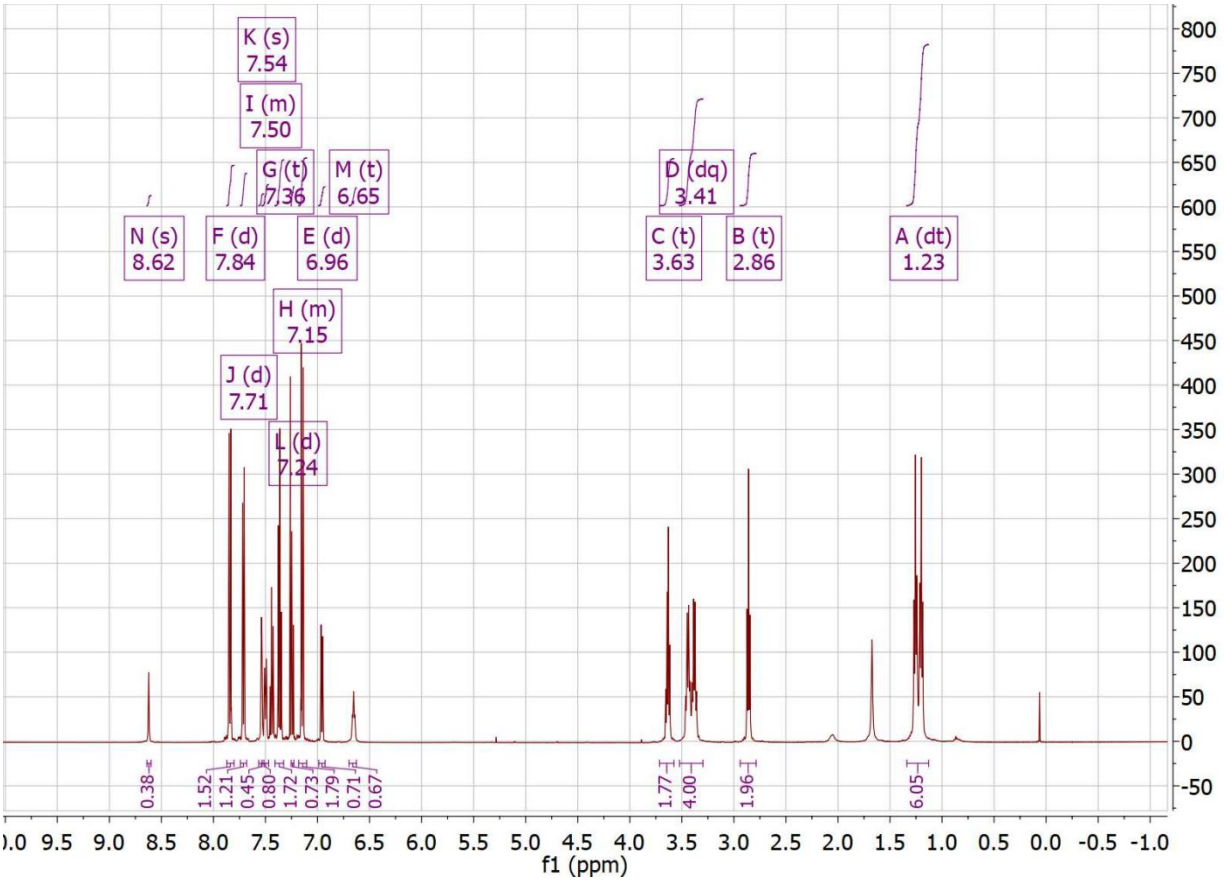
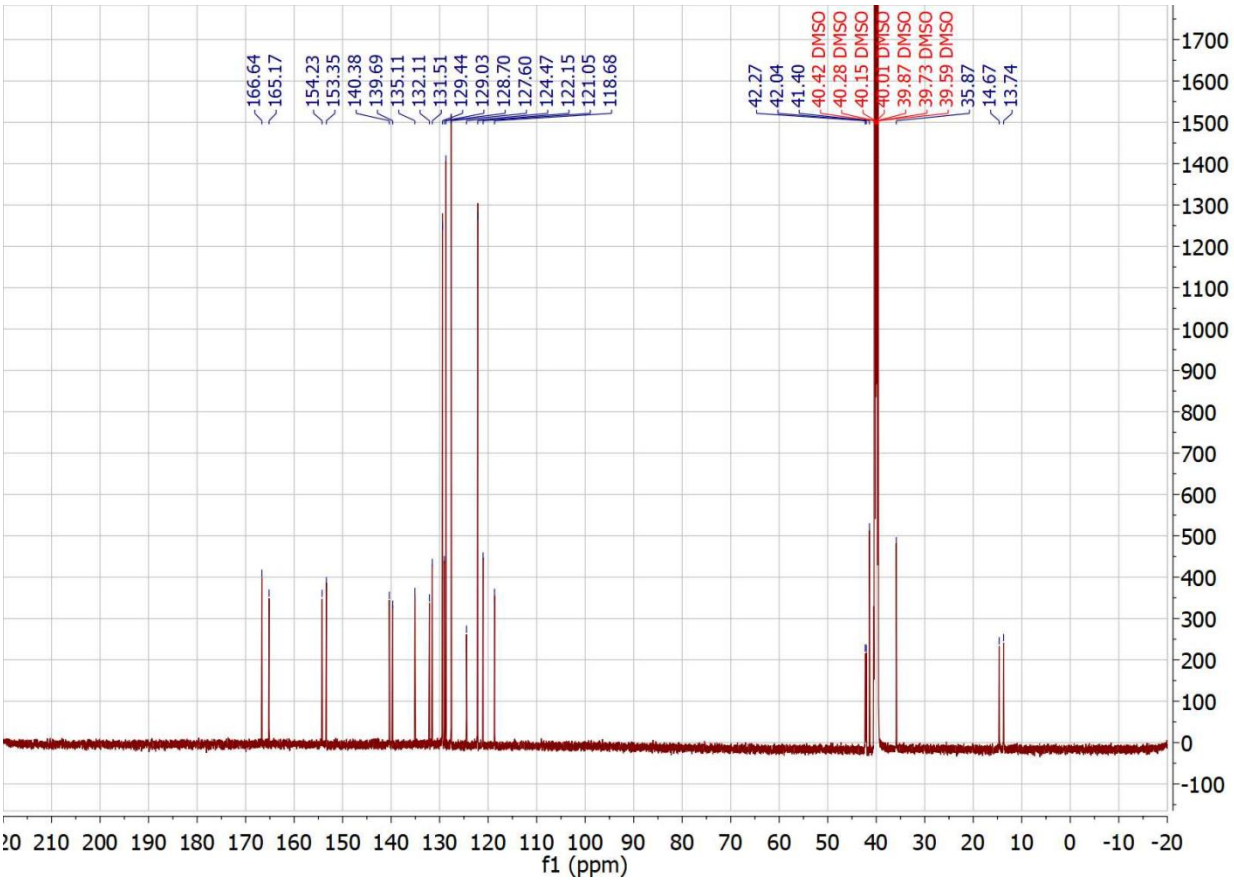
40.28 DMSO
40.14 DMSO
39.86 DMSO
39.72 DMSO
39.58 DMSO
f1 (ppm)

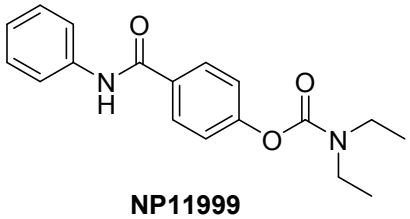


27

4-((3-(2-Benzamidoethyl)phenyl)carbamoyl)phenyl diethylcarbamate (26): To a solution of [4-[[3-(2-aminoethyl)phenyl]carbamoyl]phenyl] N,N-diethylcarbamate (200mg, 0.56mmol) in DCM (2mL) at 0°C was added benzoyl chloride (39.5mg, 0.28mmol, 0.5eq). The reaction was stirred at room temperature until complete by TLC/LCMS. The solvent was removed in vacuo and the residue purified by silica gel column chromatography using 10% methanol in dichloromethane with NH_3 to produce the title compound (**27**, 99.7mg, 38.6% yield) as a white fluffy solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 0.5H), 7.87 – 7.81 (m, 2H), 7.74 – 7.69 (m, 2H), 7.54 (q, J = 2.3 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.39 – 7.33 (m, 2H), 7.26 (d, J = 7.2 Hz, 1H), 7.18 – 7.11 (m, 2H), 6.96 (dt, J = 7.7, 1.3 Hz, 1H), 6.65 (t, J = 5.8 Hz, 1H), 3.71 – 3.58 (m, 2H), 3.41 (dq, J = 30.7, 7.1 Hz, 4H), 2.86 (t, J = 6.9 Hz, 2H), 1.23 (dt, J = 28.2, 7.1 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 167.79, 165.55, 154.15, 153.74, 139.88, 138.46, 138.38, 134.51, 131.64, 131.35, 129.18, 128.55, 128.47, 126.92, 124.94, 121.82, 120.79, 120.68, 118.77, 118.66, 42.36, 42.02, 40.99, 35.58, 14.20, 13.31. HRMS calcd for $C_{27}H_{30}O_4N_3$, 460.22308 $[M+H]^+$; found 460.22435.



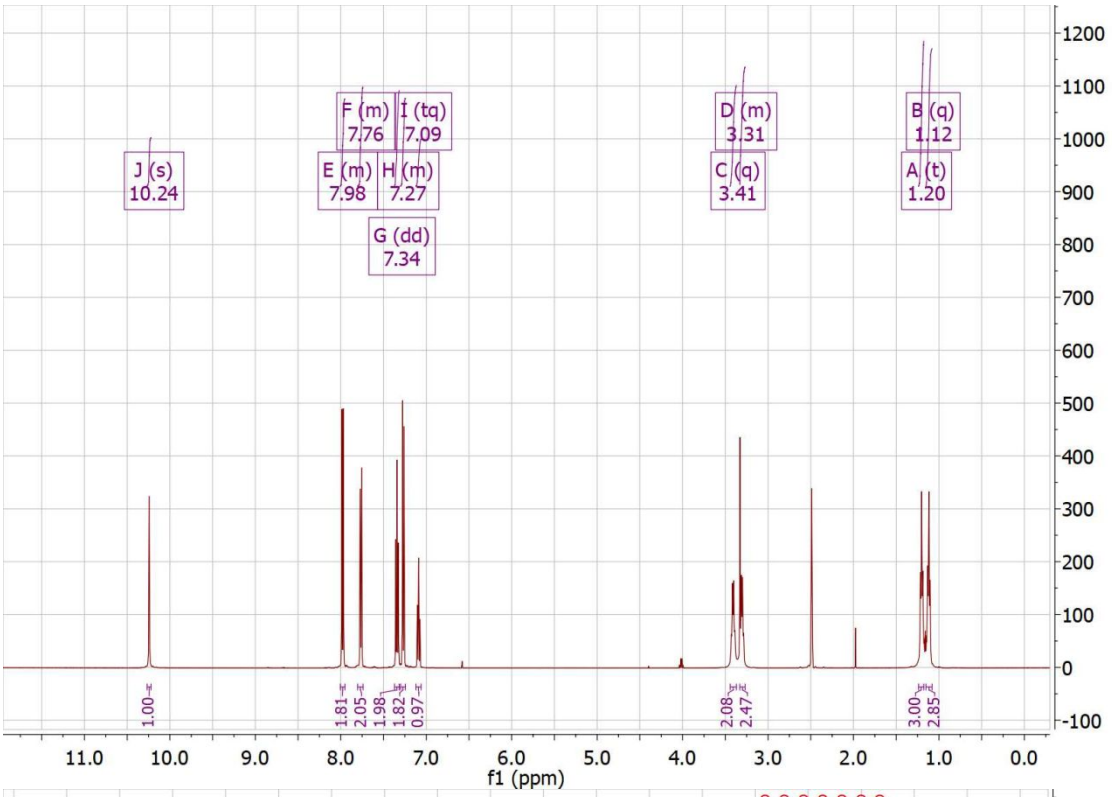


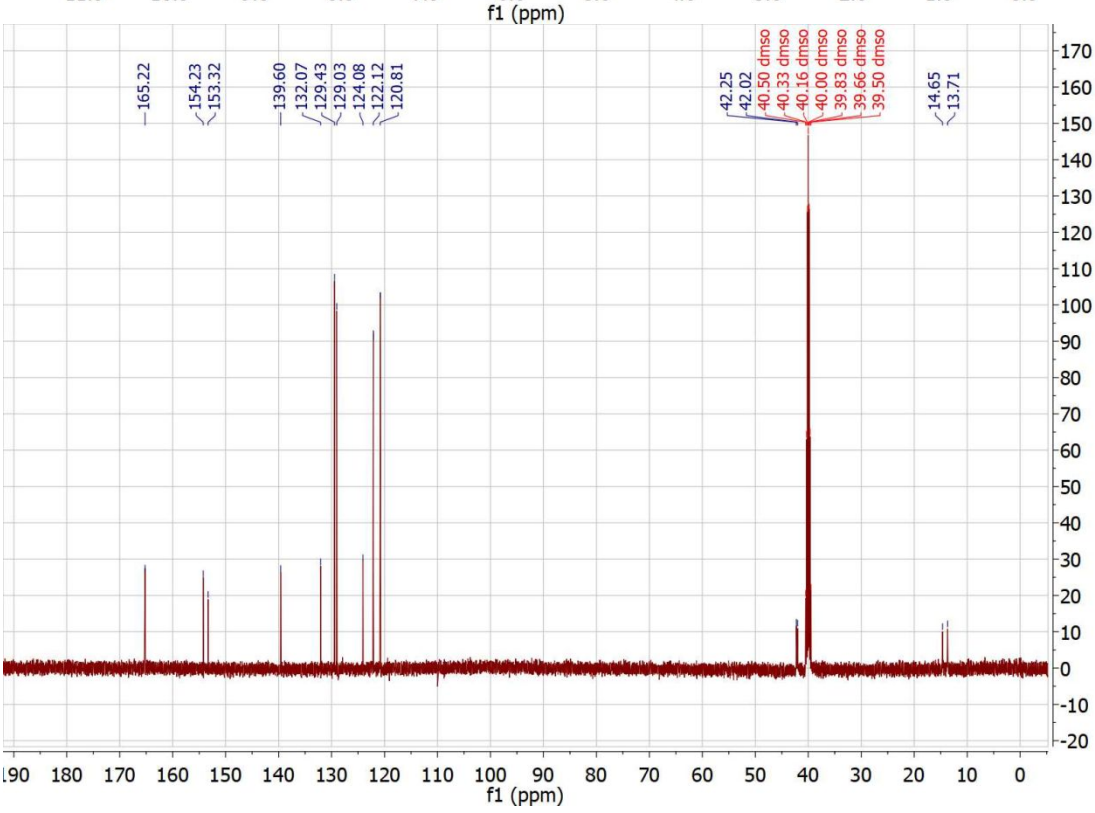


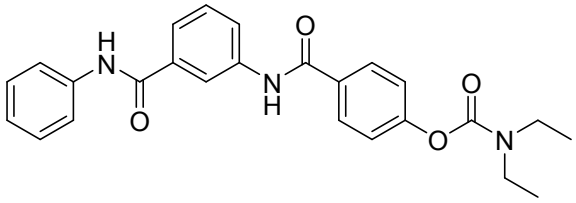
NP11999

[4-(phenylcarbamoyl)phenyl] N,N-diethylcarbamate (NP11999): To a solution of 4-(diethylcarbamoyloxy)benzoic acid (**13**, 0.20g, 0.84mmol) in DCM (10mL) was added HATU (320mg, 0.84mmol, 1.2eq), aniline (0.08mL, 0.84mmol, 1.2 eq), and N,N-diisopropylethylamine (0.15mL, 0.84mmol, 3.0eq). The reaction was stirred overnight at rt until complete by TLC. The reaction was then diluted with 1N HCl and extracted three times with DCM. The combined organic layers are washed once with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified via silica gel flash chromatography using 0-30% EtOAc in hexanes to afford the title compound (**NP11999,** 123mg, 0.62mmol, 73.3% yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.24 (s, 1H), 8.00 – 7.95 (m, 2H), 7.80 – 7.74 (m, 2H), 7.34 (dd, J = 8.4, 7.3 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.09 (tq, J = 7.3, 1.0 Hz, 1H), 3.41 (q, J = 7.1 Hz, 2H), 3.33 – 3.27 (m, 2H), 1.20 (t, J = 7.0 Hz, 3H), 1.12 (q, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d6) δ 165.22, 154.23, 153.32, 139.60, 132.07, 129.43, 129.03, 124.08, 122.12, 120.81, 42.25, 42.02,

14.65, 13.71. MP: 120-122 MP: 120-122 MP: 120-122°C. HRMS calcd for $C_{18}H_{21}O_3N_2$, 313.12467 $[M+H]^+$; found 313.15456.

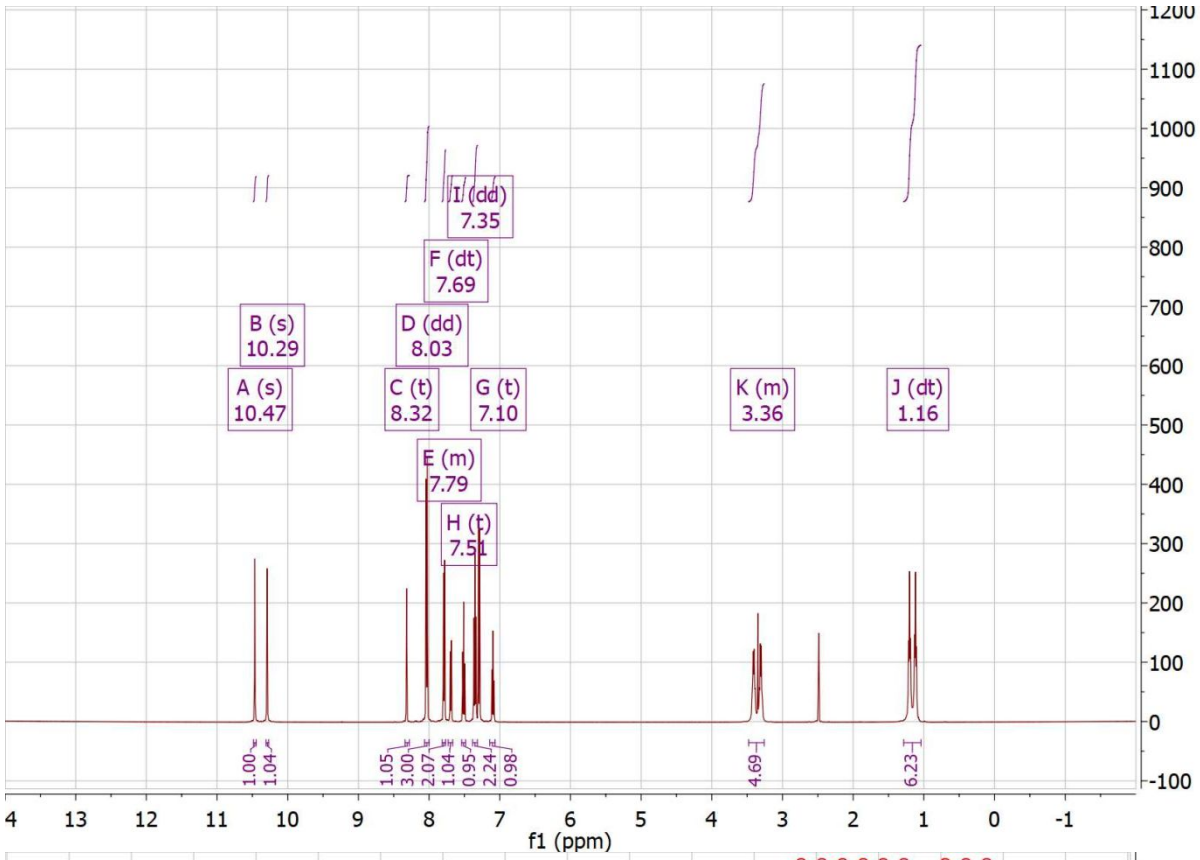






NP12000

[4-[[3-(phenylcarbamoyl)phenyl]carbamoyl]phenyl] N,N-diethylcarbamate (NP12000):
Step 1: To a solution of 4-(diethylcarbamoyloxy)benzoic acid (1.0g, 4.21mmol) in DCM (10mL) was added oxalyl chloride (2M in DCM, 2.52 mL, 1.2eq), dropwise, followed by a drop of anhydrous DMF. The mixture was stirred at room temperature for 4-6 hours until the formation of acid chloride is observed by TLC. The mixture was then concentrated in vacuo, re-dissolved in 10 mL of DCM and concentrated (2 times). The residue was then dissolved in anhydrous DCM and taken immediately into the next step.
Step 2: A solution of 4-(chlorocarbonyl)phenyl diethylcarbamate (1.0g, 1.8eq) in 5 mL DCM was added dropwise to a solution of to a solution of 3-amino-N-phenyl-benzamide (490 mg, 2.31mmol) and Et_3N (0.60mL, 4.34mmol, 1.8eq) in DCM (10 mL). The mixture was stirred at rt for 3-4 hours until complete by TLC/LCMS. The reaction was diluted with 1M HCl and extracted with DCM. The organic layer was washed once with saturated sodium bicarbonate, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified via silica gel column chromatography using 0-40% EtOAc in hexanes to produce the title compound (**NP12000**, 0.57g, 1.32mmol, 57.6 % yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 10.47 (s, 1H), 10.29 (s, 1H), 8.32 (t, J = 2.0 Hz, 1H), 8.03 (dd, J = 8.9, 2.3 Hz, 3H), 7.82 – 7.77 (m, 2H), 7.69 (dt, J = 7.8, 1.3 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.35 (dd, J = 8.5, 7.4 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 3.48 – 3.26 (m, 5H), 1.16 (dt, J = 42.2, 7.1 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.02, 165.35, 154.39, 153.31, 139.79, 139.64, 136.13, 131.75, 129.51, 129.05, 124.09, 123.74, 123.06, 122.18, 120.80, 120.41, 42.26, 42.03, 14.64, 13.70, -3.98. MP: 179-181°C. HRMS calcd for $C_{25}H_{26}O_4N_3$, 432.19178 $[M+H]^+$; found 432.19180.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A (s)
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G (t)
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K (m)
3.36
J (dt)
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E (m)
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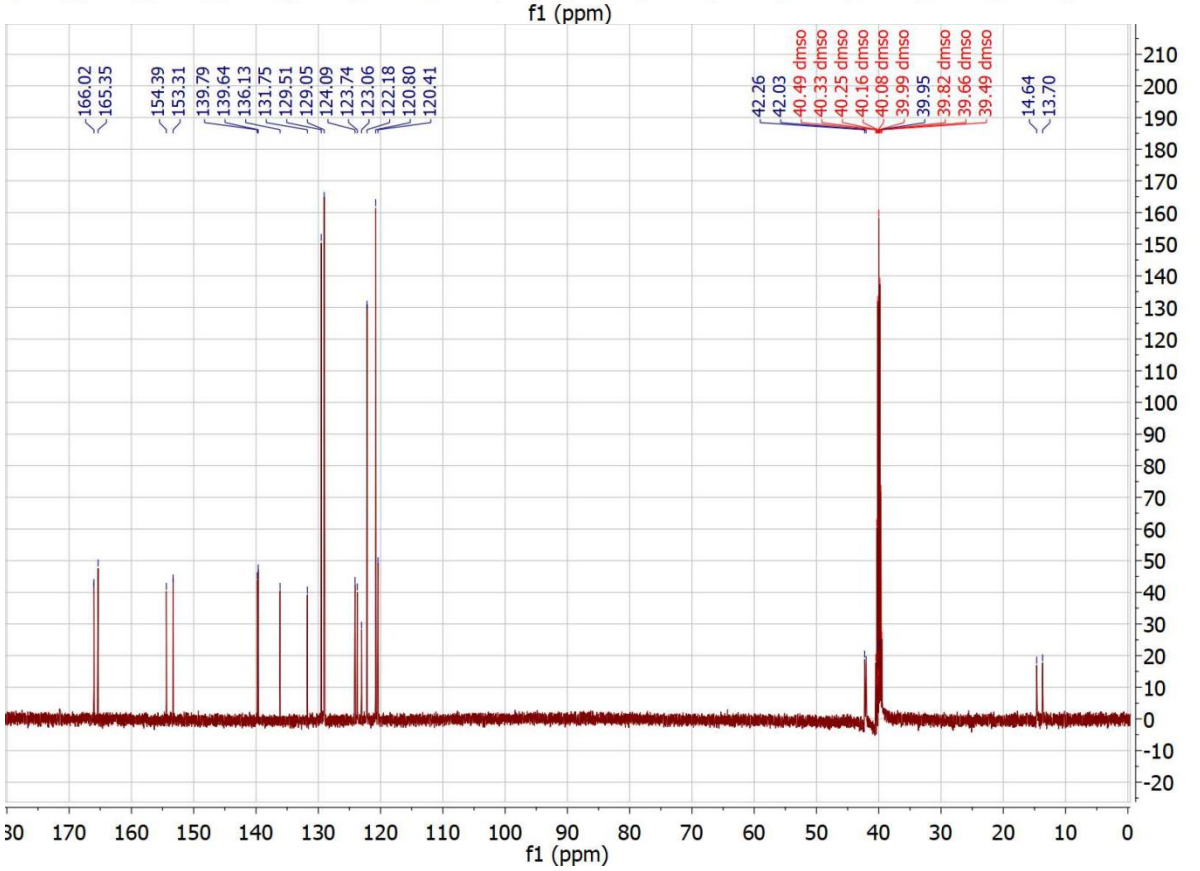
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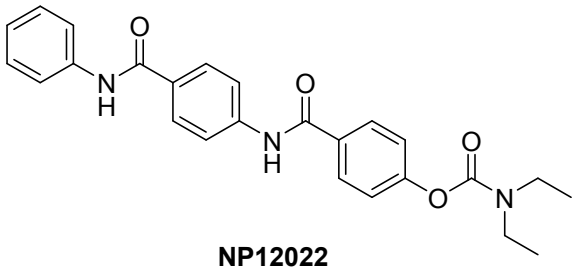
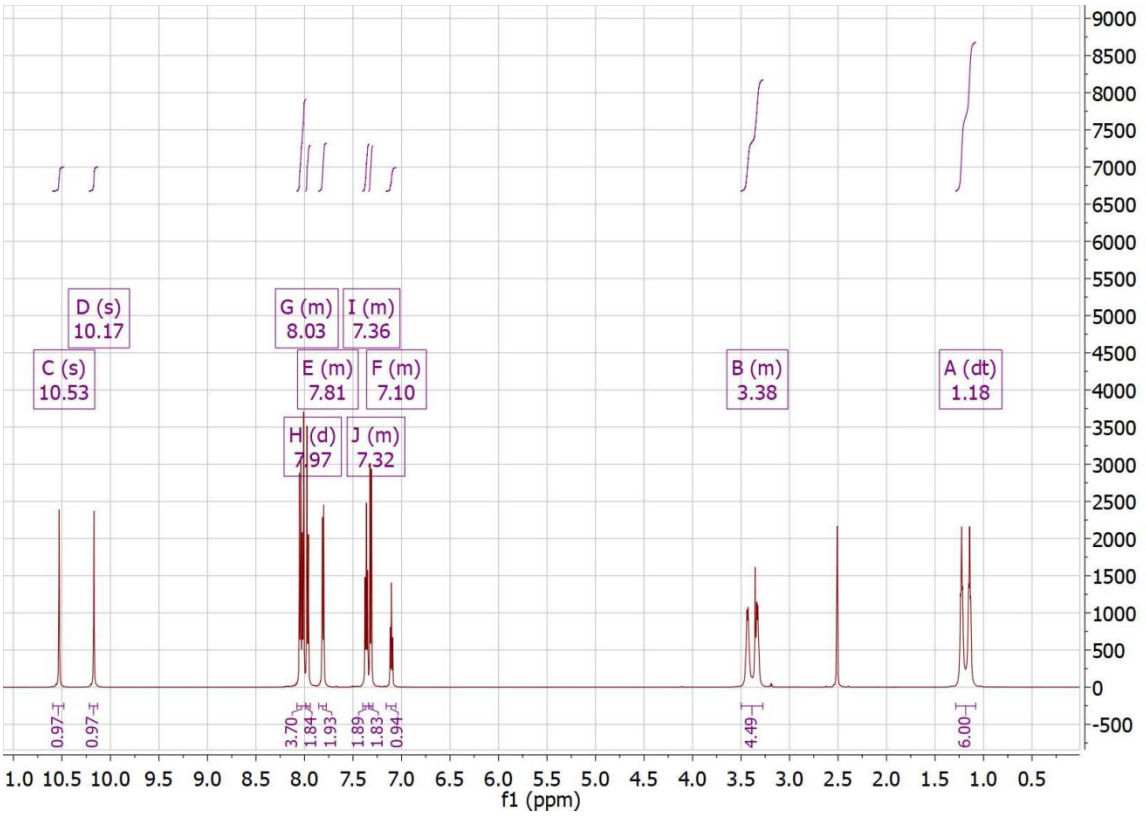
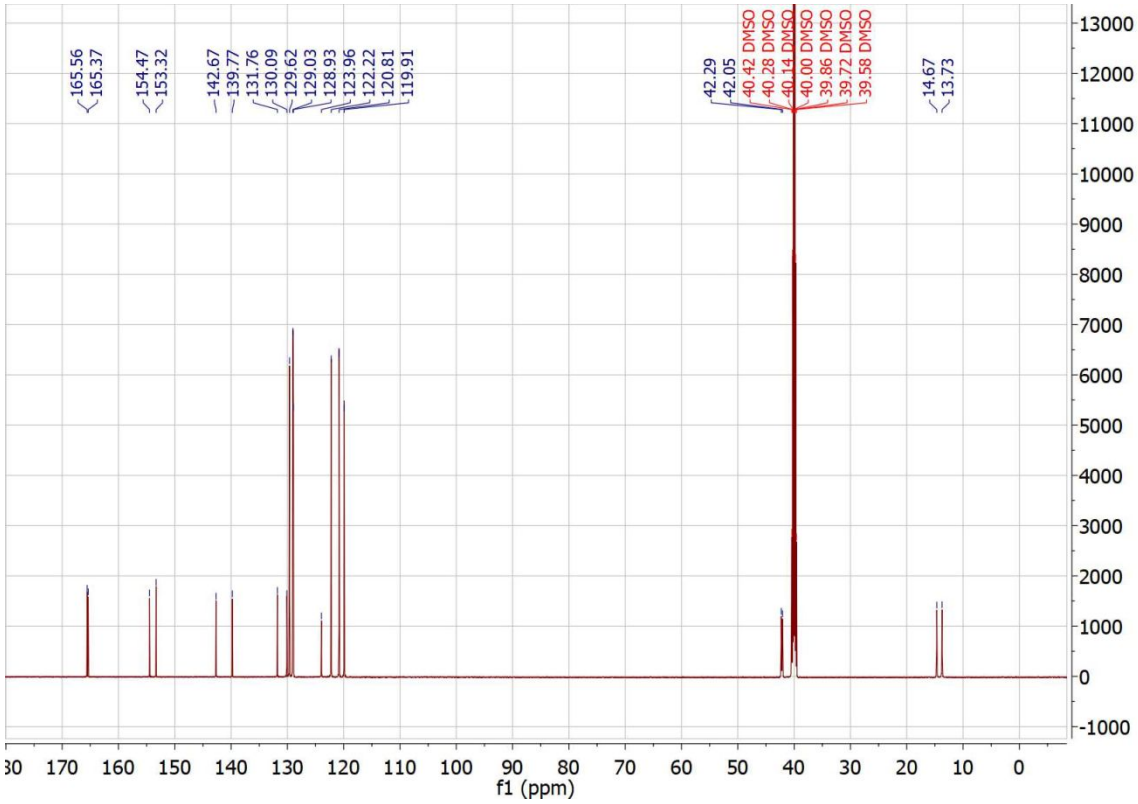


NP12022

[4-[[4-(phenylcarbamoyl)phenyl]carbamoyl]phenyl] N,N-diethylcarbamate (NP12022): A solution of 4-(chlorocarbonyl)phenyl diethylcarbamate (see **NP12000** (above) for synthesis of acid chloride, 1.0g, 4.21mmol, 1.4eq) in 5 mL DCM was added, dropwise, to a solution of 4-amino-N-phenyl-benzamide (0.75g, 3.53mmol, 1.0eq) and Et_3N (0.59mL, 4.21mmol, 1.2eq) in 10 mL DCM. This mixture was stirred overnight until complete by TLC/LCMS. The reaction mixture was diluted with 1M HCl and extracted with DCM. The organic layer is concentrated and washed with diethyl ether to yield the title compound (**NP12022**, 0.61g,1.42mmol, 40.2 % yield) as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.53 (s, 1H), 10.17 (s, 1H), 8.08 – 7.99 (m, 4H), 7.97 (d, J = 8.8 Hz, 2H), 7.85 – 7.77 (m, 2H), 7.40 – 7.34 (m, 2H), 7.34 – 7.30 (m, 2H), 7.16 – 7.06 (m, 1H), 3.50 – 3.28 (m, 4H), 1.18 (dt, J = 50.2, 7.1 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.56, 165.37, 154.47, 153.32, 142.67, 139.77, 131.76, 130.09, 129.62, 129.03, 128.93, 123.96, 122.22, 120.81, 119.91, 42.29, 42.05, 14.67, 13.73. MP 266-268°. HRMS calcd for $C_{25}H_{26}O_4N_3$, 432.19178 $[M+H]^+$; found 432.19204.

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40.00 DMSO
39.86 DMSO
39.72 DMSO
39.58 DMSO
14.67
13.73
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
30 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)