Electronic Supplementary Information (ESI)

A rapid and facile method for the general synthesis of 3-aryl substituted 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines and their ring fused analogues

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1. General:

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60-80 °C. DMF and DCM were dried over CaH_2, distilled and stored over $3A^o$ molecular sieves in sealed container. All the reactions were carried out under argon atmosphere and anhydrous conditions unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on 25 TLC aluminium sheets 20 x 20 cm Silica gel 60 F_{254}. Visualization of the developed chromatogram was performed by UV absorbance or iodine. For purification, column chromatography was performed using 60-120 or 100-200 mesh silica gel.

^1H and ^{13}C NMR spectra were recorded in 300 or 600 MHz spectrometer using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) were given from TMS (δ = 0.00) in parts per million (ppm) with the residual protons of deuterated solvent used [$CDCl_3$: ^1H NMR δ = 7.26 ppm (s); ^{13}C NMR δ = 77.0 ppm (t)]. Coupling constants (*J*) were expressed in hertz (Hz) and spin multiplicities were given as s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet) and br (broad). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using an ESI-TOF mass spectrometer. Infrared spectra were obtained as neat or KBr plate.

2. X-Ray crystallographic information of product 2"i and 3cj:

Single crystal of product **2"i** and **3cj** was obtained through slow evaporation (at room temperature) of a solution of ethylacetate in petrolium ether. A single crystal of **2"i** (or **3cj**) was attached to a glass fiber with epoxy glue and transferred to X-ray diffractometer equipped with a graphite-monochromator. Diffraction data for 3-aryl substituted 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines (**2"i**) and their ring fused analogue (**3cj)** were measured with MoKα radiation (λ = 0.71073 Å) at 296(2)K. The structures were solved by direct methods using the SHELXS-97 program.[1] Refinements were carried out with a full matrix least squares method against F^2 using SHELXL-97.[2] The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the

atom to which they were attached. The important crystal data of product **2"i** and **3cj** are given bellow.

Table 1: Important crystal data of product 2"i

Empirical formula	$C_{18}H_{15}F_3N_4$
Formula weight	344.34
Temperature	296(2) K
Wavelength	0.71073
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 7.9258(4) Å α = 90.00° b = 16.4316(8) Å β = 105.595(2) ° c = 12.9933(6) Å γ = 90.00°
Volume	1629.87(14) $Å^3$
Z	4
Density (calculated)	1.403 Mg/m^3
Absorption coefficient (Mu)	0.110 mm^{-1}
F(000)	712.0
Theta range for data collection	1.63 to 31.00°
Index ranges	-11<=h<=9, -23<=k<=23, -18<=l<=18
Reflection collected	33684
Independent reflections	10061[R(int) = 0.0310]
Completeness to theta = 25.44°	97%
Absorption correction	None
Max. and min. transmissi	0.993 and 0.995
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10061/0/452
Goodness-of-fit on F^2	1.109
Final R indices [I>2sigma(I)]	R1 = 0.0783, wR2 = 0.2102

R indices (all data)	R1 = 0.1039, wR2 = 0.2271
Largest diff. peak and hole	0.804 & -0.499 e.A^{-3}

For more details please see the CIF file attached with supporting information. The crystal data of product **2′i** has already been deposited at Cambridge Crystallographic data Centre. The CCDC reference number is 804692.

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Table 2: Important crystal data of product 3cj

Empirical formula	$C_{23}H_{25}FN_4O_2S$
Formula weight	440.54
Temperature	296(2)K
Wavelength	0.71073 A^o
Crystal System	Monoclinic
Space group	P 21/c
Unit cell dimension	a=11.4682(11) α=90.00° b=19.7219(18) β=103.607(5)° c=9.6293(9) γ = 90.00°
Volume	2116.8(3)
Z	4
Density (calculated)	1.382 Mg/m^3
Absorption coefficient (Mu)	0.190 mm^{-1}
F (000)	928.0
Crystal size	0.30x0.05x0.05 mm^{-3}
Theta range for data collection	1.83 to 24.99°
Index ranges	-13<=h<=12, -22<=k<=23, -11<=l<=11
Reflection collected	20516
Independent reflections	3724[R(int) = 0.0536]
Completeness of theta =31.55°	100%
Absorption correction	None
Max. and min. transmission	0.989 and 0.991
Refinement method	Full-matrix least-squares on F^2

Data/restraints/parameter	3724/0/282
Goodness-of-fit on F^2	1.012
Final R indices[I>2sigma(I)]	R1=0.0511, WR2=0.1436
R indices (all data)	R1=0.0423, wR2=0.1308
Largest diff. peak and hole	0.346 & -0.304 e.A^{-3}

For more details please see the corresponding CIF file attached with the supporting information. The crystal data of product **3cj** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference no is 804536.

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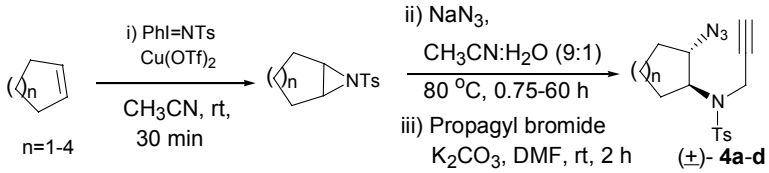
3. Preparation of the starting materials 4a-d:



a) **4a**: n=1; b) **4b**: n=2; c) **4c**: n=3; d) **4d**: n=4

Scheme 1: Synthesis of the starting materials **4a-d**

Typical procedure of *N*-propargylation leading to the synthesis of 4a: To a well-stirred solution of (±)-*trans*-2-azido-*N*-tosyl-cyclopentylamine[3i,3m] (1.00 g, 3.40 mmol), obtained from the corresponding aziridine compound[3f,3n] (Scheme 1), in dry DMF (10 mL) at 0 °C was added anhydrous K_2CO_3 (1.40 g, 10.19 mmol) and the whole reaction mixture was allowed to stir at room temperature for 1 h. Propargyl bromide (0.36 mL, 4.08 mmol) was then added at 0 °C and the reaction was allowed to stir at room temperature for another 2 h. After completion of the reaction (TLC), DMF was evaporated under reduced pressure. The resulting residue was extracted with diethyl ether (3 × 30 mL), washed with water (15 mL) and brine (10 mL) successively. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified through chromatography over silica gel (5% ethyl acetate- petroleum ether, v/v) to obtain the product **4a**.

Similarly, compounds **4b-d** were synthesized adopting the aforesaid procedure.

4. Spectral data of starting materials (4a-d):

(±)-*trans*-*N*-(2-Azido-cyclopentyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide

(4a): Yield: 82%; colorless liquid; IR (neat): υ_{max} 3289, 2964, 2103, 1597, 1339, 1158, 1093, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.61-1.88 (m, 5H), 2.00-2.04 (m, 1H), 2.23 (t, *J* = 2.1 Hz, 1H), 2.42 (s, 3H), 3.95-4.02 (m, 2H), 3.99 (dd, *J* = 2.1, 18.6 Hz, 1H), 4.26 (dd, *J* = 2.1, 18.6 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.2, 21.4, 26.5, 29.2, 33.2, 62.8, 63.8, 73.1, 79.1, 127.4, 129.4, 137.0, 143.5; MS (ESI): m/z 341.21 $[M+Na]^+$; Anal. Calcd. for $C_{15}H_{18}N_4O_2S$: C, 56.58; H, 5.70; N, 17.60. Found: C, 56.53; H, 5.74; N, 17.62.

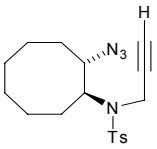
(±)-*trans*-*N*-(2-Azido-cyclohexyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (4b): Yield: 87%; colorless gum; IR (neat): υ_{max} 3288, 2938, 2862, 2099, 1597, 1449, 1337, 1262, 1159, 1091, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.22-1.27 (m, 2H), 1.37-1.39 (m, 1H), 1.68-1.80 (m, 4H), 2.13-2.16 (m, 1H), 2.21 (t, *J* = 2.4 Hz, 1H), 2.42 (s, 3H), 3.53-3.58 (m, 2H), 4.09 (dd, *J* = 2.4, 18.6 Hz, 1H), 4.15 (dd, *J* = 2.4, 18.6 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.5, 24.1, 25.0, 30.4, 31.9, 61.1, 61.6, 72.7, 79.5, 127.5, 129.3, 137.7, 143.3; MS (ESI): m/z 333.15 $[M+H]^+$, 355.12 $[M+Na]^+$; Anal. Calcd. for $C_{16}H_{20}N_4O_2S$: C, 57.81; H, 6.06; N, 16.85. Found: C, 57.83; H, 6.09; N, 16.81.

(±)-*trans*-*N*-(2-Azido-cycloheptyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide (4c): Yield: 94%; white solid, m.p.: 69-71 °C; IR (KBr): υ_{max} 3266, 2935, 2861, 2492, 2098, 1595, 1442, 1342, 1239, 1159, 1442, 1342, 1239, 1159, 1093, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.40-1.43 (m, 3H), 1.67-1.84 (m, 7H), 2.22 (s, 1H), 2.42 (s, 3H), 3.65-3.71 (m, 1H), 3.88-3.92 (m, 1H), 3.96 (d, *J* = 19.8 Hz, 1H), 4.23 (d, *J* = 18.6 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.80 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 21.9, 25.7, 27.8, 30.2, 31.0, 33.9, 64.2, 64.7,

72.8, 79.3, 127.4, 129.3, 137.5, 143.3; MS (EI): m/z 346.2 $[M+H]^+$; Anal. Calcd. for $C_{17}H_{22}N_4O_2S$: C, 58.94; H, 6.40; N, 16.17. Found: C, 58.97; H, 6.43; N, 16.12.

(±)-*trans*-*N*-(2-Azido-cyclooctyl)-4-methyl-*N*-prop-2-ynyl-benzenesulfonamide(4d):

Yield: 77%; off-white solid, m.p.: 71-73 ^oC; IR (KBr): υ_{max} 3291, 2932, 2863, 2098, 1597, 1447, 1342, 1294, 1158, 1094, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.46-1.86 (m, 10H), 1.91-2.04 (m, 2H), 2.23 (t, *J* = 2.4 Hz, 1H), 2.42 (s, 3H), 3.92 (dd, *J* = 2.4, 18.6 Hz, 1H), 3.92 (br, 2H), 4.21 (dd, *J* = 2.4, 18.6 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 21.9, 24.7, 26.3, 27.4, 27.5, 31.0, 61.3, 63.2, 72.6, 79.4, 127.5, 129.2, 137.5, 143.2; MS (FAB+): m/z 361 $[M+H]^+$, 383 $[M+Na]^+$; Anal. Calcd. for $C_{18}H_{24}N_4O_2S$: C, 59.97; H, 6.71; N, 15.54. Found: C, 59.99; H, 6.73; N, 15.51.

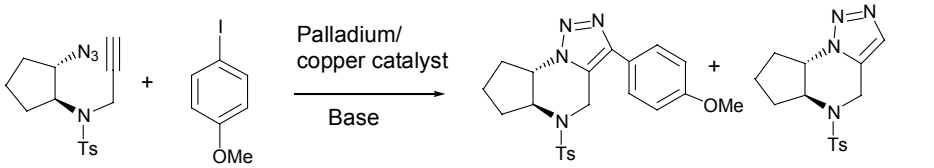


5. Optimisation of reaction conditions (screening studies):

Initially, we studied the model reaction using *trans*-azido-alkyne **4a** and *p*-methoxy iodide **5a** as substrates. The results are summarized in Table-1 as shown below. Our initial attempt to effect the desired cycloaddition utilizing Et_3N (base) and Sonogashira's catalyst [$Pd(PPh_3)_2Cl_2$/CuI], used usually in C-C bond formations,[4] afforded the *trans*-fused product **3aa** (10%) along with the self-cycloadduct (32%) of **4a** (entry 1, Table 1). Employing a stronger base, the yield of the targeted product **3aa** improved marginally (16%); the side product was still formed to the extent of 24% (entry 2, Table 1). Replacement of the palladium(II) catalyst by $Pd(PPh_3)_4$ also failed to improve the reaction outcome satisfactorily (entries 3-4, Table 1). However, when we employed $Pd(OAc)_2/PPh_3$ as catalyst and CuI as cocatalyst along with Et_3N as base, the reaction was found to be complete within 5 h with moderate yield (39%) of the desired product **3aa** along with small amount (16%) of self-cycloadduct of **4a** (entry 5, Table 1). To our delight, replacement of Et_3N by a stronger base like K_2CO_3 provided the targeted product **3aa** exclusively (68% yield) with complete suppression of side product formation (entry 6, Table 1). The copper free reaction was found to be extremely slow for the coupling of alkyne **4a** with aryl iodide **5a**, while omission of PPh_3 did not allow the coupling significantly (see entries 7-8, Table 1). Thus, the CuI/PPh_3 co-catalytic

combination appeared to be important along with $Pd(OAc)_2$ as catalyst. It is noteworthy that immediate heating without stirring at room temperature for sometime (1.25 h) led

Table 1: Optimization of the reaction conditions for the synthesis of product **3aa**[a]



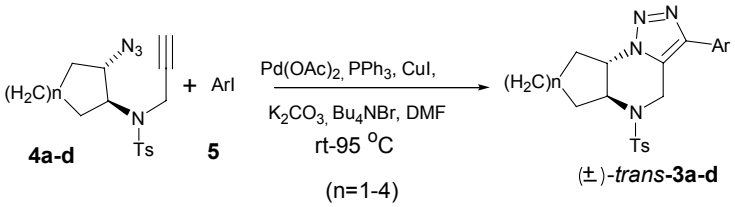
(±)-*trans* **4a** **5a** (±)-*trans* -**3aa** self-cycloadduct of **4a**

Entry	Catalyst	Base[b]	Time[c] (h) (rt + heating)	Yield (%)[d] 3aa	Yield (%)[d] self-cycloadduct
1.	$Pd(PPh_3)_2Cl_2/CuI$	Et_3N	1+11	10	32
2.	$Pd(PPh_3)_2Cl_2/CuI$	K_2CO_3	1.25 + 6	16	24
3.	$Pd(PPh_3)_4/CuI$	Et_3N	1.5 + 9	20	22
4.	$Pd(PPh_3)_4/CuI$	K_2CO_3	0.75 + 13	24	29
5.	$Pd(OAc)_2/PPh_3/CuI$	Et_3N	2 + 3	39	16
6.	**$Pd(OAc)_2/PPh_3/CuI$**	**K_2CO_3**	**1.25 + 1**	**68**	**0**
7.[e]	$Pd(OAc)_2/PPh_3$	K_2CO_3	16 + 1.5	17	23
8.[e]	$Pd(OAc)_2/CuI$	K_2CO_3	2.15 + 0.75	5	34

[a]Azido-alkyne **4a** (1.1 mmol), *p*-methoxyphenyl iodide **5a** (1.0 mmol), Palladium catalyst (5 mol%), CuI (10 mol%, except entry 7), PPh_3 (20 mol%), Base (3.0 mmol) in DMF (4 mL) stirred at room temp for hour(s) followed by heating at 95 ^{O}C.[b]Catalytic amount of Bu_4NBr (10 mol%) was used in case of K_2CO_3 as base. [c]Time indicated the consumption of the starting materials/intermediate based on TLC.[d]Yields of isolated pure products.
[e]Self cycloadduct was formed at rt and iodo compound **5a** was recovered (3% for entry 7 and 43 % for entry 8).

to the formation of the undesired self cycloadduct predominantly. DMF was found to be the solvent of choice in these reactions. However, Et_3N and K_2CO_3 appeared to be superior among the bases examined. The *trans* stereochemistry of the product **3aa** was easily deduced from the coupling constants (δ 2.84, ddd, J = 9.8, 11.6 and 6.5 Hz, 1H; δ 4.19, ddd, J = 10.2, 10.2 and 7.4 Hz, 1H) of the ring juncture methine protons in the ^{1}H-NMR.

6. Synthesis of fused analogues of 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines (3):



a) **3a**, **4a**: n=1; b) **3b**, **4b**: n=2; c) **3c, 4c**: n=3; d) **3d, 4d**: n=4

Scheme 2: Synthesis of Products **3a-d**

General procedure for the synthesis of product 3a-d:

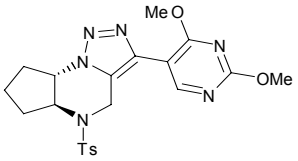
A mixture of $Pd(OAc)_2$ (9.6 mg, 0.043 mmol, 5 mol%) and PPh_3 (44.8 mg, 0.171 mmol, 20 mol%) in dry DMF (1 mL) was stirred at rt for 10 min under argon atmosphere. Iodo-compound **5** (0.855 mmol), K_2CO_3 (235.9 mg, 1.709 mmol) and tetrabutylammonium bromide (13.8 mg, 0.043 mmol, 5 mol%) were then added successively and the whole reaction mixture was allowed to stir at rt for another 10 min. A solution of azido-acetylene **4** (0.940 mmol) in dry DMF (2 mL) was added drop-wise followed by the addition of CuI (16.3 mg, 0.085 mmol, 10 mol%). The resulting mixture was flushed with argon carefully and stirred for the specified time (as shown in Table 1 of the text) at rt. After disappearance of starting materials (monitored by TLC), the whole mixture was allowed to heat at 95 °C for the requisite time period (as shown in Table 1 of the text). Upon completion of the reaction (TLC), the solvent was removed in vacuo; the residue was mixed with water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography (ethyl acetate-petroleum ether).

7. Spectral data of the (±)-*trans*-fused products 3a-d:

(±)-*trans*-(5a,8a)-3-Phenyl-5-(toluene-4-sulfonyl)-5,5a,6,7,8,8a-hexahydro-4*H*-cyclopenta[e][1,2,3]triazolo[1,5-*a*][1,4]pyrazine (3ab): Yield: 47%; white solid, m.p.: 186-188 ^{o}C; IR (KBr): υ_{max} 3431, 2964, 2880, 2098, 1599, 1495, 1448, 1354, 1164, 1088, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.96-2.00 (m, 2H), 2.09-2.12 (m, 1H), 2.20-2.28 (m, 1H), 2.38-2.47 (m, 1H), 2.42 (s, 3H), 2.68-2.72 (m, 1H), 2.85 (ddd, *J* = 6.4, 10.8, 10.8 Hz, 1H), 4.20 (ddd, *J* = 7.8, 10.2, 10.2 Hz, 1H), 4.40 (d, *J* = 15.6 Hz, 1H), 5.21 (d, *J* = 15.6 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.6, 21.5, 23.9, 27.4, 45.1, 62.3, 62.5, 126.1, 126.3, 127.6, 128.1, 128.9, 130.1, 130.5, 133.2, 142.2, 144.6; ESI-MS: m/z 395.08 $[M+H]^+$, 417.08 $[M+Na]^+$; Anal. Calcd. for $C_{21}H_{22}N_4O_2S$: C, 63.94; H, 5.62; N, 14.20. Found: C, 63.97; H, 5.63; N, 14.17.

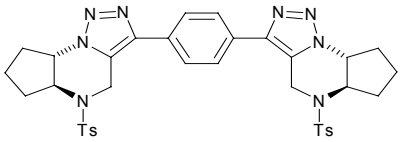
(±)-*trans*-(5a,8a)-3-Pyridin-3-yl-5-(toluene-4-sulfonyl)-5,5a,6,7,8,8a-hexahydro-4*H*-cyclopenta[e][1,2,3]triazolo[1,5-*a*][1,4]pyrazine (3ac): Yield: 71%; white solid, m.p.: 186-188 ^{o}C; IR (KBr): υ_{max} 3426, 2962, 2098, 1598, 1452, 1350, 1163, 1089, 1032, 1003 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.9-1.12 (m, 3H), 2.22-2.42 (m, 2H), 2.42 (s, 3H), 2.67-2.76 (m, 1H), 2.81-2.87 (m, 1H), 4.19-4.29 (m, 1H), 4.35 (d, *J* = 15.6 Hz, 1H), 5.24 (d, *J* = 15.6 Hz, 1H), 7.33 (d, *J* = 6.9 Hz, 2H), 7.44 (br, 1H), 7.73 (d, *J* = 7.8 Hz, 2H), 8.14 (d, *J* = 5.7 Hz, 1H), 8.68-8.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.7, 21.5, 24.0, 27.3, 45.2, 62.4, 62.6, 126.9, 127.7, 130.2, 132.8, 133.7, 139.2, 144.8, 147.0, 149.2; MS (ESI): m/z 396.11 $[M+H]^+$, 418.07 $[M+Na]^+$; HRMS Calcd. for $C_{20}H_{22}N_5O_2S$ $[M+H]^+$ 396.1494, found 396.1522.

(±)-*trans*-(5a,8a)-3-(2,4-Dimethoxy-pyrimidin-5-yl)-5-(toluene-4-sulfonyl)-5,5a,6,7,8,8a-hexahydro-4*H*-cyclopenta[e][1,2,3]triazolo[1,5-*a*][1,4]pyrazine (3ad): Yield: 50%;



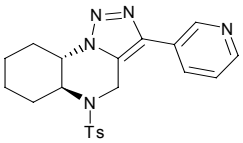
brown solid, m.p.: 170-172 ^{o}C; IR (KBr): υ_{max} 3404, 2924, 2857, 1614, 1560, 1476, 1354, 1281, 1164, 1084, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.92-1.99 (m, 2H), 2.07-2.15 (m, 1H), 2.27-2.29 (m, 1H), 2.40-2.42 (m, 1H), 2.44 (s, 3H), 2.69-2.71 (m, 1H), 2.87 (ddd, *J* = 6.6, 9.9, 11.7 Hz, 1H), 4.07 (s, 6H), 4.17 (d, *J* = 16.2 Hz, 1H), 4.16-4.19 (m, 1H), 5.04 (d, *J* = 16.2 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 19.7, 21.6, 24.0, 27.4, 45.5, 54.0, 55.2, 62.4, 62.6, 106.0, 127.7, 127.9, 130.1, 132.1, 133.2, 135.5, 144.7, 158.8, 165.3, 167.1; MS (ESI): m/z 456.98 $[M+H]^+$, 478.97 $[M+Na]^+$; Anal. Calcd. for $C_{21}H_{24}N_6O_4S$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.22; H, 5.36; N, 18.45.

(±)-1,4-Bis((5a,8a-*trans*)-5-(toluene-4-sulfonyl)-5,5a,6,7,8,8a-hexahydro-4*H*-cyclopenta[e][1,2,3]triazolo[1,5-*a*][1,4]pyrazin-3-yl)-benzene (3af): Yield 44%; light brown



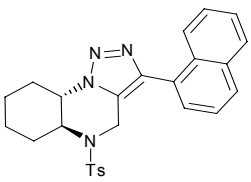
solid, m.p.: 162-164 ^{o}C; IR (KBr): υ_{max} 3428, 2963, 2102, 1598, 1348, 1160, 1091, 1047 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.60-1.68 (m, 2H), 1.74-1.76 (m, 2H), 1.81-1.88 (m, 1H), 1.91-1.99 (m, 3H), 2.01-2.09 (m, 2H), 2.13-2.25 (m, 1H), 2.40 (s, 3H), 2.43 (s, 3H), 2.68-2.27 (m, 1H), 2.86 (ddd, *J* = 6.0, 10.5, 10.5 Hz, 1H), 4.07 (q, *J* = 8.0 Hz, 1H), 4.15 (q, *J* = 9.0 Hz, 1H), 4.18-4.23 (m, 1H), 4.28 (d, *J* = 19.2 Hz, 1H), 4.37 (d, *J* = 15.6 Hz, 1H), 4.49 (d, *J* = 18.6 Hz, 1H), 5.21 (d, *J* = 15.6 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19. 7, 20.5, 21.6, 24.0, 27.0, 27.4, 29.3, 29.7, 34.2, 45.2, 62.4, 63.2, 64.1, 125.9, 126.5, 127.7, 128.5, 128.5, 129.5, 130.2, 131.9, 132.1, 133.2, 137.4, 144.8; MS (FAB+): m/z 711.3 $[M+H]^+$; MS (ESI): m/z 711 $[M+H]^+$, 732.91 $[M+Na]^+$; HRMS Calcd. for $C_{36}H_{39}N_8O_4S_2$ $[M+H]^+$ 711.2536, found 711.2535.

(±)-*trans*-(5a,9a)-3-Pyridin-3-yl-5-(toluene-4-sulfonyl)-4,5,5a,6,7,8,9,9a-octahydro-[1,2,3]triazolo[1,5-*a*]quinoxaline (3bc): Yield: 77%; yellow solid, m.p.: 198-200 ^{o}C; IR



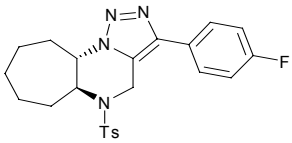
(KBr): υ_{max} 3428, 3041, 2945, 2866, 1595, 1450, 1349, 1159, 1092, 1002 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35-1.68 (m, 3H), 1.93-2.07 (m, 3H), 2.37 (s, 3H), 2.37-2.43 (m, 1H), 2.99-3.04 (m, 1H), 3.24-3.31 (m, 1H), 3.98-4.05 (m, 1H), 4.72 (d, *J* = 17.1 Hz, 1H), 5.31 (d, *J* = 17.1 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 2H), 7.44-7.50 (br, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 8.06 (d, *J* = 7.2 Hz, 1H), 8.66 (br, 1H), 8.85 (br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.5, 23.6, 25.2, 29.9, 30.3, 43.7, 59.4, 62.4, 126.8, 127.4, 129.9, 136.8, 144.3; MS (ESI): m/z 410.13 $[M+H]^+$, 432.13 $[M+Na]^+$; HRMS Calcd. for $C_{21}H_{24}N_5O_2S$ $[M+H]^+$ 410.1651, found 410.1648.

(±)-*trans*-(5a,9a)-3-Naphthalen-1-yl-5-(toluene-4-sulfonyl)-4,5,5a,6,7,8,9,9a-octahydro[1,2,3]triazolo[1,5-*a*]quinoxaline (3bg): Yield**:** 47%; white solid**,** m.p.: 142-144 ^{o}C;



IR (KBr): υ_{max} 3046, 2936, 2862, 2097, 1595, 1449, 1342, 1158, 1088, 1002 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.37-1.43 (m, 1H), 1.48-1.55 (m, 1H), 1.66-1.73 (m, 1H), 1.96-1.98 (m, 2H), 2.01-2.05 (m, 1H), 2.32 (s, 3H), 2.42-2.47 (m, 1H), 3.05-3.07 (m, 1H), 3.30 (ddd, *J* = 3.0, 11.2, 11.2 Hz, 1H), 4.02 (ddd, *J* = 4.0, 10.9, 10.9 Hz, 1H), 4.61 (d, *J* = 17.4 Hz, 1H), 5.06 (d, *J* = 16.8 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.39-7.42 (m, 3H), 7.53-7.58 (m, 3H), 7.94 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.5, 23.7, 25.3, 29.9, 30.7, 43.6, 59.2, 62.7, 125.2, 125.7, 126.2, 126.6, 126.8, 127.3, 127.4, 128.3, 128.5, 129.2, 129.9, 131.4, 134.0, 136.6, 141.6, 144.1; ESI-MS: m/z 459.14 $[M+H]^+$, 481.11 $[M+Na]^+$; Anal. Calcd. for $C_{26}H_{26}N_4O_2S$: C, 68.10; H, 5.71; N, 12.22. Found: C, 68.08; H, 5.74; N, .12.19.

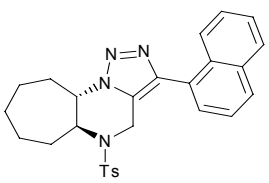
(±)-*trans*-(5a,10a)-3-(4-Fluoro-phenyl)-5-(toluene-4-sulfonyl)-5,5a,6,7,8,9,10,10a-octa-hydro-4*H*-cyclohepta[e][1,2,3]triazolo[1,5-*a*][1,4]pyrazine (3cj): Yield: 51%; white



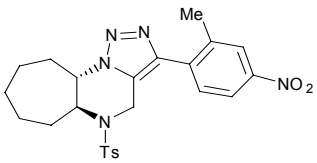
solid, m.p.: 214-216 ^{o}C; IR (KBr): υ_{max} 3071, 2929, 2861, 1595, 1505, 1454, 1339, 1221, 1158, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.63-1.81 (m, 6H), 1.90-1.93 (m, 1H), 2.03-2.09 (m, 1H), 2.32 (s, 3H), 2.39-2.44 (m, 1H), 3.11-3.15 (m, 1H), 3.81 (ddd, *J* = 3.0, 10.0, 10.0

Hz, 1H), 4.00 (ddd, *J* = 3.4, 10.0, 10.0 Hz, 1H), 4.67 (d, *J* = 16.8 Hz, 1H), 4.96 (d, *J* = 16.8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 9.0 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 9.6 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.5, 24.3, 24.5, 24.9, 29.5, 33.0, 40.5, 59.9, 61.9, 115.8, 116.1, 126.5, 126.7, 127.5, 127.9, 128.0, 129.6, 135.7, 141.4, 143.9, 160.9, 164.2; MS (EI): m/z 440 [M^+]; HRMS Calcd. for $C_{23}H_{26}FN_4O_2S$ $[M+H]^+$ 441.1760, found 441.1773.

(±)-*trans*-(5a,10a)-3-Naphthalen-1-yl-5-(toluene-4-sulfonyl)-5,5a,6,7,8,9,10,10a-octa-hydro-4*H*-cyclohepta[e][1,2,3]triazolo[1,5-*a*][1,4]pyrazine (3cg): Yield: 52%; off-white solid, m.p.: 180-182 °C; IR (KBr): υ_{max} 3440, 3047, 2924, 2862, 1594, 1450, 1345, 1159, 1094 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.70-1.79 (m, 4H), 1.80-1.87 (m, 2H), 1.94-1.98 (m, 1H), 2.09-2.14 (m, 1H), 2.33 (s, 3H), 2.42-2.46 (m, 1H), 3.20-3.24 (m, 1H), 3.82 (ddd, *J* = 3.4, 10.2, 10.2 Hz, 1H), 4.15 (ddd, *J* = 3.2, 9.7, 9.7 Hz, 1H), 4.66 (d, *J* = 17.4 Hz, 1H), 4.80 (d, *J* = 17.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.38 (dd, *J* = 0.9, 6.9 Hz, 1H), 7.52-7.58 (m, 3H), 7.93-7.95 (m, 2H), 8.13 (dd, *J* = 1.8, 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.5, 24.3, 24.7, 25.0, 29.7, 32.9, 40.90, 60.2, 62.2, 125.3, 125.7, 126.2, 126.6, 127.1, 127.3, 128.5, 129.2, 129.4, 129.8, 131.2, 134.0, 136.0, 142.1, 143.8; MS (FAB+): m/z 473 $[M+H]^+$, 495 $[M+Na]^+$; Anal. Calcd. for $C_{27}H_{28}N_4O_2S$: C, 68.62; H, 5.97; N, 11.85. Found: C, 68.59; H, 6.01; N, 11.91.

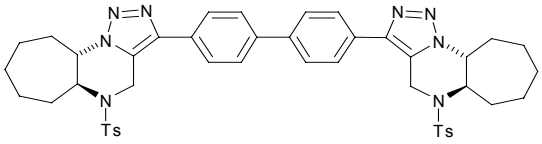


(±)-*trans*-(5a,10a)-3-(2-Methyl-4-nitro-phenyl)-5-(toluene-4-sulfonyl)-5,5a,6,7,8,9,10, 10a-octahydro-4*H*-cyclohepta[e][1,2,3]triazolo[1,5-*a*][1,4]pyrazine (3ck): Yield: 48%; yellow solid, m.p.: 207-209 °C; IR (KBr): υ_{max} 3428, 2932, 2866, 1595, 1518, 1452, 1343, 1160, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.71-1.80 (m, 6H) ,1.94-1.96 (m, 1H), 2.08-2.11 (m, 1H), 2.38 (br, 4H), 2.49 (s, 3H), 3.16-3.20 (m, 1H), 3.79 (ddd, *J* = 3.1, 9.9, 9.9 Hz, 1H), 4.17 (ddd, *J* = 3.3, 9.3, 9.3 Hz, 1H), 4.66 (d, *J* = 17.1 Hz, 1H), 4.75 (d, *J* = 17.1 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.33-7.38 (m, 3H), 8.14 (dd, *J* = 1.8, 7.8 Hz, 1H), 8.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.8, 21.5, 23.9, 24.5, 24.9, 29.6, 32.3, 40.9, 60.5, 62.2, 121.0, 125.8, 126.6, 129.7, 129.8, 130.1, 135.8, 136.4, 138.7, 140.6, 144.08,



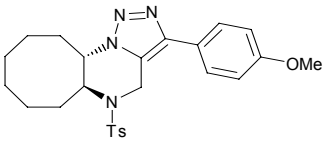
147.3; MS (FAB+): m/z 482 [M+H]; Anal. Calcd. for $C_{24}H_{27}N_5O_4S$: C, 59.86; H, 5.65; N, 14.54. Found: C, 59.83; H, 5.67; N, 14.51.

(±)-4,4'-Bis-((5a,10a-*trans*)-5-(toluene-4-sulfonyl)-5,5a,6,7,8,9,10,10a-octahydro-4*H*-cyclohepta[e][1,2,3]triazolo[1,5-*a*][1,4]pyrazin-3-yl)-biphenyl (3cl): Yield: 71%; off-



white solid, m.p.: > 300 °C; IR (KBr): υ_{max} 3442, 2928, 2861, 1600, 1492, 1452, 1347, 1159, 1091, 1001 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.68-1.81 (m, 12H), 1.91-1.92 (m, 2H), 2.03-2.20 (m, 2H), 2.32 (s, 6H), 2.34-2.42 (m, 2H), 3.10-3.12 (m, 2H), 3.83 (ddd, *J* = 3.0, 9.9, 9.9 Hz, 2H), 4.02 (ddd, *J* = 3.0, 9.6, 9.6 Hz, 2H), 4.72 (d, *J* = 16.8 Hz, 2H), 5.05 (d, *J* = 16.8 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 4H), 7.26 (d, *J* = 8.4 Hz, 4H), 7.66 (d, *J* = 8.4 Hz, 4H), 7.78 (d, *J* = 7.8 Hz, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.4, 24.3, 24.5, 24.8, 29.5, 29.6, 33.1, 40.5, 59.9, 61.8, 126.5, 126.8, 127.5, 127.9, 129.5, 129.6, 135.5, 140.0, 142.0, 144.0; MS (FAB+): m/z 843 $[M+H]^+$; HRMS Calcd. for $C_{46}H_{51}N_8O_4S_2$ $[M+H]^+$ 843.3475, found 843.3450.

(±)-*trans*-(5a,11a)-3-(4-Methoxy-phenyl)-5-(toluene-4-sulfonyl)-4,5,5a,6,7,8,9,10,11,11a-decahydrocycloocta[e][1,2,3]triazolo[1,5-*a*][1,4]pyrazine (3da): Yield: 46%;



white solid, m.p.: 158-160 °C; IR (KBr): υ_{max} 2927, 2097, 1616, 1508, 1450, 1345, 1297 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.43-1.47 (m, 1H) ,1.61-1.85 (m, 8H), 2.03-2.11 (m, 2H), 2.32 (s, 3H), 2.83-2.86 (m, 1H), 3.88 (s, 3H), 4.18 (ddd, *J* = 5.2, 10.9, 5.2 Hz, 1H), 4.36 (ddd, *J* = 5.2, 10.9, 5.2 Hz, 1H), 4.49 (d, *J* = 16.8 Hz, 1H), 5.20 (d, *J* = 16.8 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H)**;** ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.5, 22.5, 23.1, 26.5, 26.8, 26.9, 31.8, 33.9, 38.0, 54.9, 55.4, 56.6, 114.5, 123.1, 126.4, 126.6, 127.4, 127.7, 129.6, 135.6, 142.1, 144.0, 159.6; MS (FAB+): m/z 467 $[M+H]^+$; Anal. Calcd. for $C_{25}H_{30}N_4O_3S$: C, 64.35; H, 6.48; N, 12.01. Found: C, 64.32; H, 6.51; N, 11.99.

8. Detosylation of some of the products (3aa, 3ae, 3bc) synthesized:

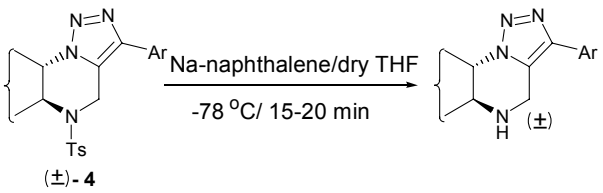
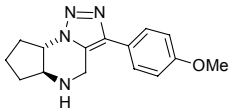
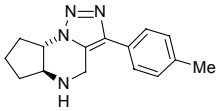
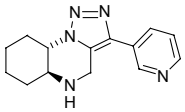


Table-2. Detosylation of Some of the Products **4**[a,b]

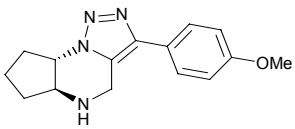
Entry	Tosylated compound	Product	Yield[c]
1.	**3aa**		61%
2.	**3ae**		70%
3.	**3bc**		72%

[a]Tosylated compound **3** (0.244 mmol), Naphthalene (5.38 mmol), Na (4.89 mmol) in dry THF (6 mL) stirred at -78 °C for 10-15 min. [b]All products are in racemic mixture. [c]Yields of the isolated pure products.

General procedure for detosylation[5a-b]**:** Sodium (112.6 mg, 4.89 mmol) was added to a solution of naphthalene (689.3 mg, 5.38 mmol) in dry THF (5 mL). After stirring for 2 h at room temperature, a green solution was appeared. In another flask, to a well-stired solution of tosylated compound (**3aa**/**3ae**/**3bc**) (0.244 mmol) in dry THF (3 mL) was added the aforesaid green solution dropwise at -78 °C. The whole reaction mixture was then allowed to stir at -78 °C for 10-15 min. After consumption of the starting materials (TLC), the reaction mixture was quenched with 2-3 drops of water and extracted with ethyl acetate (3 × 30 mL). The organic extracts were evaporated and the resulting residue was purified through silica gel (100-200 mesh) column chromatography (70-75% ethyl acetate in petroleum ether) to afford the detosylated product.

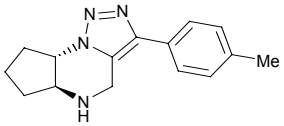
9. Spectral data of the detosylated products:

Detosylated product of 3aa: Yield: 61%; off-white solid, m.p.: 179-181 ^{o}C; IR (KBr): υ_{max} 3307, 2958, 1612, 1553, 1501, 1458, 1374, 1299, 1248, 1183, 1034, 1007 cm^{-1}; ^{1}H



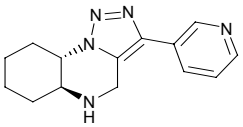
NMR ($CDCl_3$, 600 MHz): δ 1.56-1.63 (m, 1H), 1.90-1.97 (m, 1H), 2.00-2.05 (m, 2H), 2.09-2.13 (m, 1H), 2.67-2.71 (m, 1H), 2.95-3.00 (m, 1H), 3.75-3.80 (m, 1H), 3.84 (s, 3H), 4.36 (d, *J* = 16.2 Hz, 1H), 4.52 (d, *J* = 16.2 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 19.3, 25.4, 26.4, 43.9, 55.3, 62.4, 63.1, 114.2, 124.1, 127.4, 141.6, 159.1; MS (EI): m/z 270 [M^+]; HRMS Calcd. for $C_{15}H_{19}N_4O$ $[M+H]^+$ 271.1559, found 271.1602.

Detosylated product of 3ae: Yield: 70%; off-white solid, m.p.: 145-147 ^{o}C; IR (KBr): υ_{max} 3307, 2958, 2871, 1640, 1500, 1460, 1375, 1304, 1232, 1139, 1055, 1005 cm^{-1}; ^{1}H



NMR ($CDCl_3$, 600 MHz): δ 1.55-1.62 (m, 1H), 1.81-1.95 (m, 1H), 1.96-1.99 (m, 2H), 2.09-2.14 (m, 1H), 2.38 (s, 3H), 2.67-2.72 (m, 1H), 2.97 (ddd, *J* = 6.7, 10.0, 11.5 Hz, 1H), 3.74-3.79 (m, 1H), 4.36 (d, *J* = 16.2 Hz, 1H), 4.53 (d, *J* = 16.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 19.3, 21.2, 25.3, 26.3, 43.9, 62.4, 63.1, 126.0, 127.9, 128.6, 129.5, 137.4, 141.7; MS (EI): m/z 254 [M^+]; Anal. Calcd. for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03. Found: C, 70.79; H, 7.18; N, 22.09.

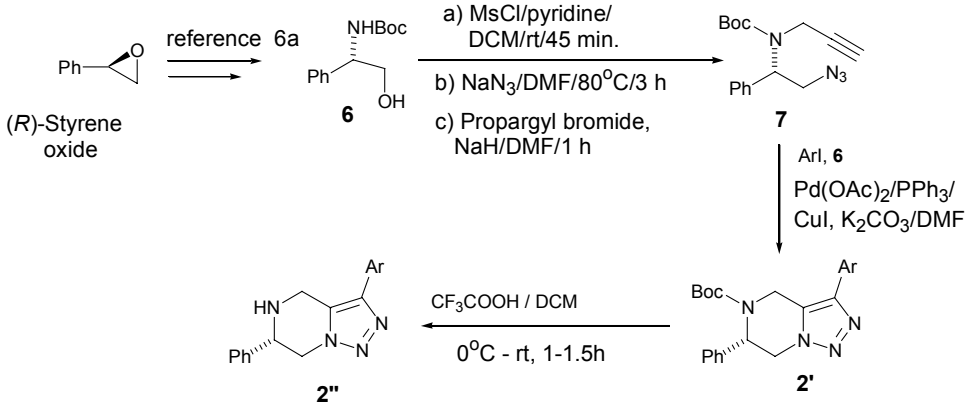
Detosylated product of 3bc: Yield: 71%; off-white solid, m.p.: 168-170 ^{o}C; IR (KBr): υ_{max} 3422, 3307, 2938, 2858, 1638, 1473, 1312, 1125, 1001 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600



MHz): δ 1.43-1.49 (m, 2H), 1.50-1.64 (m, 2H), 1.90-1.93 (m, 1H), 1.99-2.01 (m, 1H), 2.08-2.09 (m, 1H), 2.75 (ddd, *J* = 3.6, 10.0, 10.0 Hz, 1H), 3.05-3.06 (m, 1H), 3.86 (ddd, *J* = 3.4, 10.2, 10.2 Hz, 1H), 4.37 (d, *J* = 15.6 Hz, 1H), 4.46 (d, *J* = 15.6 Hz, 1H), 7.39 (dd, *J* = 4.8, 7.8 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 2H), 8.56 (d, *J* = 3.6 Hz, 1H), 8.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 24.2, 24.5, 28.8, 31.2, 42.5, 58.5, 63.3, 123.8, 127.7, 129.1, 133.5, 138.5, 146.9,

148.6; ESI-MS: m/z 256.10 $[M+H]^+$, 278.07 $[M+Na]^+$; HRMS Calcd. for $C_{14}H_{18}N_5$ $[M+H]^+$ 256.1562, found 256.1557.

10. Preparation of optically active 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines 2′ and 2″:



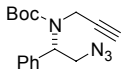
Scheme-4

Synthesis of the alcohol **6** was performed according to the literature procedure[6a], starting from commercially available (*R*)-styrene oxide. The requisite azido-acetylene **7** was obtained from alcohol **6** using three-step protocol[6a-b] as depicted in Scheme 4. The targeted compounds **2′**was synthesised easily using the optimized reaction conditions. The BOC-group was then deprotected by the treatment TFA leading to the formation of amine **2″**.

Typical procedure of *N*-propargylation leading to the synthesis of substrate 7: To a suspension of sodium hydride (0.114 g, 2.86 mmol, 60% dispersion in mineral oil) in dry DMF (2 mL) under ice-cooled conditions was added a solution of the Boc protected azido-amine (0.50 g, 1.90 mmol) in dry DMF (3 mL) dropwise and stirring was continued for 30 min. Propargyl bromide (0.22 mL, 2.48 mmol) was then added to the reaction mixture drop-wise at 0 ^oC and allowed to reach to rt over 30 min. After completion of the reaction (TLC), it was quenched with saturated NH_4Cl solution and extracted with diethyl ether (3 × 30 mL). Combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was

removed and resulting residue was purified through silica gel (100-200 mesh) column chromatography (1% ethyl acetate-pet ether, v/v) to afford the compound **7** (82%).

(S)-*tert*-Butyl-2-azido-1-phenyl-ethyl(prop-2-ynyl)carbamate (7): Yield: 82%; colorless gum; IR (neat): υ_{max} 3298, 2977, 2930, 2102, 1696, 1449, 1366, 1252, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.49 (m, 9H), 2.21 (s, 1H), 3.60 (d, J = 17.4 Hz, 1H), 3.89 (dd, J = 6.6, 12.3 Hz, 1H), 3.99-4.09 (m, 2H), 5.32 (br, 1H), 7.30-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.3, 33.8, 51.3, 58.1, 71.1, 80.5, 81.2, 127.5, 128.1, 128.2, 128.7, 136.9, 154.8; MS (FAB+): m/z 301 $[M+H]^+$; Anal. Calcd. for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.01; H, 6.73; N, 18.62.

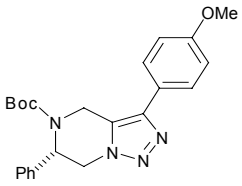


General procedure for preparation of optically active 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazines 2´:

A mixture of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol%) and PPh_3 (26.2 mg, 0.1 mmol, 20 mol%) in dry DMF (3 mL) was stirred at rt for 10 min under argon atmosphere. Iodo-compound **5** (0.5 mmol), K_2CO_3 (138 mg, 1.0 mmol) and tetrabutylammonium bromide (8.06 mg, 0.025 mmol, 5 mol%) were then added successively. The whole reaction mixture was allowed to stir at rt for another 10 minutes under argon atmosphere. A solution of azido-acetylene **7** (165.2 mg, 0.55 mmol) in dry DMF (2 mL) was added dropwise, followed by addition of CuI (9.5 mg, 0.05 mmol). The resulting mixture was flushed with argon carefully and stirred at room temperature for specified time (See Table 2 of the text). After disappearance of starting materials (TLC), the whole mixture was allowed to heat at 95 °C for requisite time (see Table 2 of the text). Upon completion of the reaction (TLC), the solvent was removed in vacuo; the residue was mixed with water (10 mL) and then extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography (ethyl acetate-pet ether) to afford the desired product.

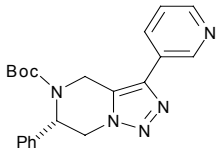
11. Spectral data of the optically active products 2′a-n:

(6*S*)-*tert*-Butyl-3-(4-methoxy-phenyl)-6-phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[1,5-*a*] pyrazine-5-carboxylate (2′a): Yield: 43%; white solid, m.p.: 204-206 ^{o}C; $[\alpha]_D^{20}$ +15.84



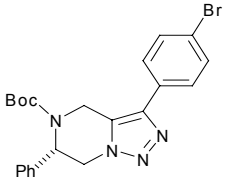
(c 0.1, $CHCl_3$); IR (KBr): υ_{max} 2978, 2837, 1692, 1514, 1452, 1403, 1302, 1247, 1170, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.55 (s, 9H), 3.83 (s, 3H), 4.17 (d, *J* = 17.1 Hz, 1H), 4.66 (dd, *J* = 4.5, 13.5 Hz, 1H), 5.21 (d, *J* = 13.8 Hz, 1H), 5.29 (d, *J* = 17.7 Hz, 1H), 5.97 (br, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 4.8 Hz, 2H), 7.26 (br, 3H), 7.60 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.3, 37.9, 47.9, 51.0, 55.3, 82.0, 114.3, 123.3, 125.5, 126.4, 127.3, 128.3, 129.07, 129.1, 136.1, 141.6, 154.3, 159.3; ESI-MS: m/z 407.07 $[M+H]^+$, 429.05 $[M+Na]^+$; Anal. Calcd. for $C_{23}H_{26}N_4O_3$: C, 67.96; H, 6.45; N, 13.78. Found: C, 67.93; H, 6.49; N, 13.75.

(6*S*)-*tert*-Butyl-6-phenyl-3-pyridin-3-yl-6,7-dihydro-4*H*-[1,2,3]triazolo[1,5-*a*]pyra-zine-5-carbo-xylate (2′c): Yield: 74%; off-white solid, m.p.: 144-146 ^{o}C; $[\alpha]_D^{20}$ +7.54 (c



0.15, $CHCl_3$); IR (KBr): υ_{max} 2980, 1698, 1454, 1398, 1302, 1245, 1164, 1001 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.56 (s, 9H), 3.22 (d, *J* = 17.1 Hz, 1H), 4.69 (dd, *J* = 3.7, 13.3 Hz, 1H), 5.28 (d, *J* = 13.8 Hz, 1H), 5.36 (d, *J* = 17.4 Hz, 1H), 6.03 (br, 1H), 7.11 (br, 2H), 7.29-7.56 (m, 4H), 7.97 (d, *J* = 7.5 Hz, 1H), 8.58-8.62 (m, 1H), 8.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.3, 37.7, 47.9, 51.0, 82.2, 123.7, 126.2, 128.3, 128.5, 129.1, 131.6, 133.0, 133.2, 135.7, 138.7, 146.8, 148.8 154.1; MS (ESI): m/z 378.08 $[M+H]^+$, 400.05 $[M+Na]^+$; HRMS Calcd. for $C_{21}H_{24}N_5O_2$ $[M+H]^+$ 378.1930, found 378.1933.

(6*S*)-*tert*-Butyl-3-(4-bromo-phenyl)-6-phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[1,5-*a*]-pyrazine-5-carboxylate (2′n): Yield: 50%; white solid, m.p.: 200-201 ^{o}C; $[\alpha]_D^{20}$ +11.28



(c 0.1, $CHCl_3$); IR (KBr): υ_{max} 2977, 1698, 1503, 1455, 1402, 1370, 1299, 1244, 1164, 1095, 1003 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.56 (s, 9H), 4.16 (d, *J* = 16.8 Hz, 1H), 4.67 (dd, *J* = 4.6, 13.3 Hz, 1H), 5.23 (d, *J* = 13.8 Hz, 1H), 5.29 (d, *J* = 18.0 Hz, 1H), 5.98 (br, 1H), 7.10

(d, J = 5.7 Hz, 2H), 7.28 (br, 3H), 7.54 (br, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.3, 37.8, 47.9, 51.0, 82.1, 121.8, 126.3, 126.4, 127.4, 128.3, 129.1, 129.6, 131.9, 135.8, 140.6, 154.1; MS (FAB+): m/z 455 and 457 $[M+H]^+$; HRMS Calcd. for $C_{22}H_{23}BrN_4O_2Na$ $[M+Na]^+$ 477.0902, found 477.0919.

12. Synthesis of Boc-deprotected products 2":

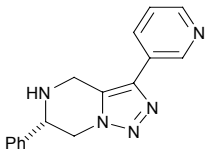
General procedure for Boc-deprotection:

To a solution of Boc-protected product **2′** (0.135 mmol) in dry DCM (2 mL) was added trifluoroacetic acid (0.1 mL, 1.35 mmol) at 0 ^{o}C under argon gas atmosphere. The whole reaction mixture was allowed to reach to rt during 1-1.5 h. After completion of the reaction (TLC), the solvent was evaporated to dryness; residue was treated with saturated $NaHCO_3$ followed by extraction with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified through silica gel (100-200 mesh) column chromatography (20-30% ethyl acetate-pet ether) to afford the product **2"**.

13. Spectral data of products 2"a-n:

(6*S*)-6-Phenyl-3-pyridin-3-yl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazine (2″c):

Yield: 89%; light yellow solid, m.p.: 165-167 ^{o}C; $[\alpha]_D^{20}$ +124.64 (c 0.1, $CHCl_3$); IR



(KBr): υ_{max} 3302, 3031, 2933, 2808, 1685, 1566, 1458, 1410, 1324, 1199, 1002 cm^{-1}; ^{1}H NMR (pyridine-d_5, 600 MHz): δ 4.21 (dd, J = 3.9, 11.1 Hz, 1H), 4.32 (t, J = 10.5 Hz, 1H), 4.40 (d, J = 16.2 Hz, 1H), 4.67 (d, J = 15.6 Hz, 1H), 4.81 (dd, J = 3.0, 12.0 Hz, 1H), 7.36-7.39 (m, 2H), 7.44 (t, J = 7.2 Hz, 3H), 7.64 (d, J = 7.8 Hz, 2H), 8.28 (dd, J = 1.8, 7.8 Hz, 1H), 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 42.4, 52.8, 57.1, 123.9, 126.8, 127.5, 128.6, 128.9, 129.1, 133.5, 138.5, 138.5, 146.9, 148.8; MS (FAB+): m/z 278 $[M+H]^+$, 300 $[M+Na]^+$; HRMS Calcd. for $C_{16}H_{15}N_5$ $[M^+]$ 277.1327, found 277.1293.

(6*S*)-6-Phenyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*] pyrazine (2″i): Yield: 81%; off-white solid, m.p.: 190-191 ^{o}C; $[\alpha]_D^{20}$ +117.64 (c 0.1, $CHCl_3$); IR (KBr): υ_{max} 3301, 3236, 3067, 2941, 1681, 1617, 1451, 1329, 1242, 1167, 1125, 1069 cm^{-1}; ^{1}H NMR (pyridine-d_5, 600 MHz): δ 4.23 (dd, *J* = 3.3, 10.5 Hz, 1H), 4.33 (t, *J* = 11.7 Hz, 1H), 4.44 (d, *J* = 16.2 Hz, 1H), 4.72 (d, *J* = 16.2 Hz, 1H), 4.83 (dd, *J* = 3.6, 12.0 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 2H), 8.12 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 42.5, 52.8, 57.0, 123.2, 125.0, 125.8, 125.8, 125.8, 126.1, 126.8, 128.8, 128.9, 129.1, 129.3, 138.5, 140.1; MS (FAB+): m/z 345 $[M+H]^+$, 367 $[M+Na]^+$; HRMS Calcd. for $C_{18}H_{15}F_3N_4$ $[M^+]$ 344.1249, found 344.1248.

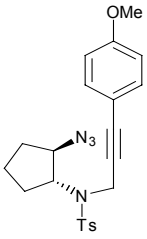
(6*S*)-3-(4-Fluoro-phenyl)-6-phenyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazine (2″j): Yield: 88%; white solid, m.p.: 169-171 ^{o}C; $[\alpha]_D^{20}$ +118.16 (c 0.1, $CHCl_3$); IR (KBr): υ_{max} 3275, 3066, 2889, 1608, 1560, 1502, 1326, 1232, 1159, 1098, 1010 cm^{-1}; ^{1}H NMR (pyridine-d_5, 600 MHz): δ 4.19 (m, 1H), 4.30 (t, *J* = 11.4 Hz, 1H), 4.37 (dd, *J* = 1.8, 15.6 Hz, 1H), 4.63 (d, *J* = 15.6 Hz, 1H), 4.79 (dd, *J* = 3.0, 12.0 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.36-7.39 (m, 1H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.99 (t, *J* = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 42.4, 52.8, 57.1, 115.8, 115.9, 126.8, 127.5, 127.5, 127,7, 127.7, 127.8, 128.8, 129.1, 138.7, 140.6, 161.5, 163.1; MS (FAB+): m/z 295 $[M+H]^+$; HRMS Calcd. for $C_{17}H_{15}FN_4$ $[M^+]$ 294.1281, found 294.1304.

14. Spectral data of self-cycloadduct of substrate 4a and intermediate internal alkyne D:

Self-cycloadduct of Substrate 4a: White solid, m.p.: 181-183 ^{o}C; IR (KBr): υ_{max} 3613, 3273, 3141, 2964, 2882, 1597, 1451, 1344, 1160, 1094, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.86-1.99 (m, 2H), 2.07-2.09 (m, 1H), 2.24-2.28 (m, 1H), 2.34-2.43 (m, 1H), 2.44 (s, 3H), 2.65-2.71 (m, 1H), 2.79 (ddd, *J* = 6.6, 10.2, 12.0 Hz, 1H), 4.13-4.18 (m, 1H), 4.17 (d, *J* = 15.6 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H),

7.36 (d, *J* = 7.8 Hz, 2H), 7.52 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 19.6, 21.5, 23.9, 27.3, 44.3, 62.2, 62.6, 127.0, 127.7, 129.5, 129.7, 130.1, 132.9, 143.5, 144.6; MS (ESI): m/z 319.08 $[M+H]^+$, 341.06 $[M+Na]^+$; Anal. Calcd. for $C_{15}H_{18}N_4O_2S$: C, 56.58; H, 5.70; N, 17.60. Found: C, 56.55; H, 5.74; N, 17.54.

(±)-*trans*-*N*-(2-Azido-cyclopentyl)-*N*-[3-(4-methoxy-phenyl)-prop-2-ynyl]-4-methyl-benzenesulfonamide (D): Yield: 65%; colorless liquid; IR (neat): υ_{max} 2924, 2101, 1606, 1506, 1446, 1342, 1251, 1159, 1094 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.63-1.75 (m, 3H), 1.81-1.91 (m, 2H), 2.00-2.06 (m, 1H), 2.38 (s, 3H), 3.81 (s, 3H), 4.06-4.15 (m, 2H), 4.23 (d, *J* = 18.6 Hz, 1H), 4.45 (d, *J* = 18.9 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.85 (d, *J* = 7.8 Hz, 2H); MS (ESI): m/z 447.19 $[M+Na]^+$, 463.17 $[M+K]^+$; Anal. Calcd. for $C_{22}H_{24}N_4O_3S$: C, 62.24; H, 5.70; N, 13.20. Found: C, 62.20; H, 5.74; N, 13.26.



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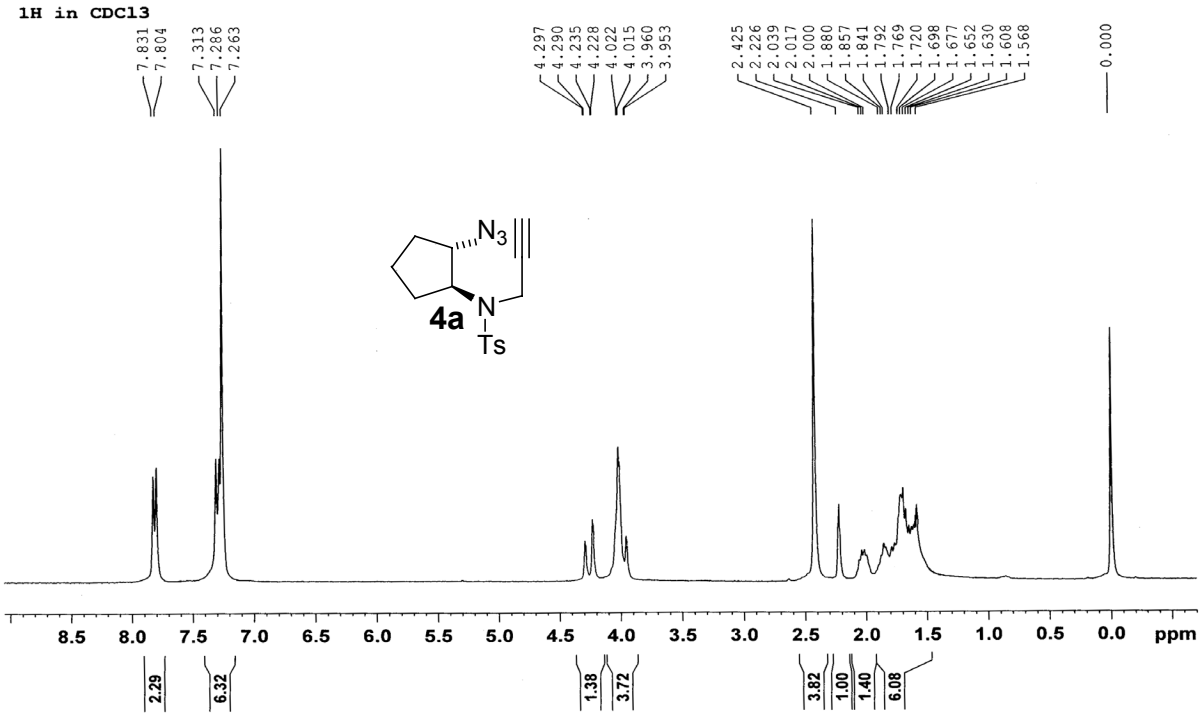
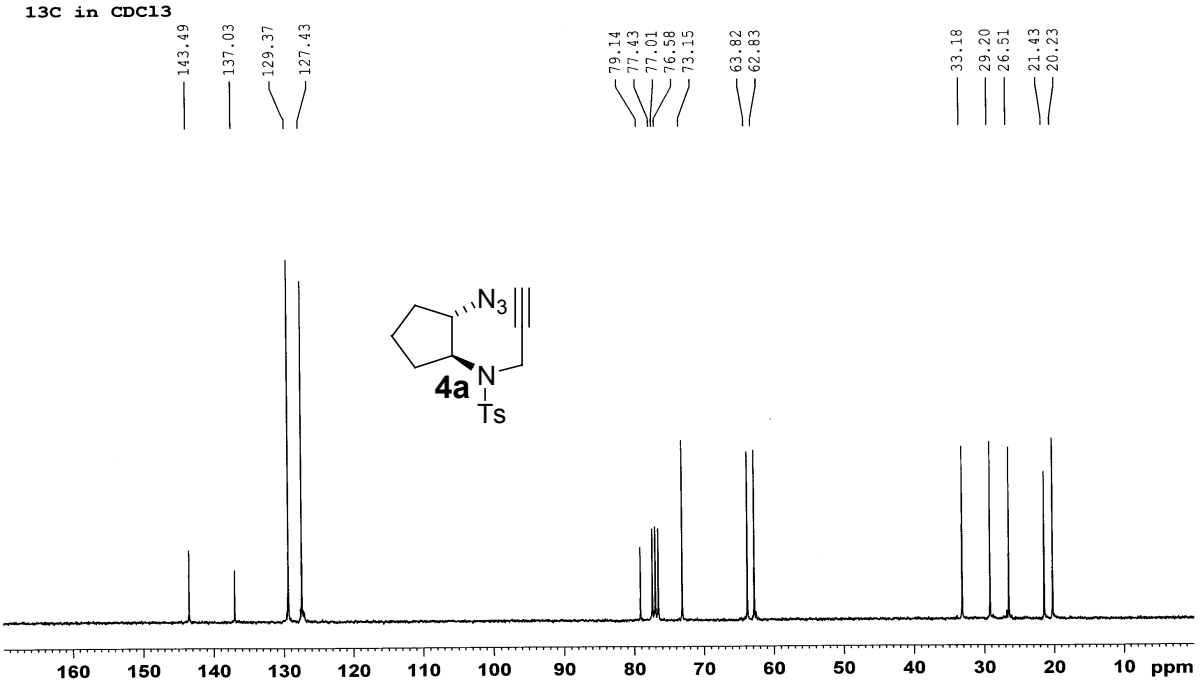
16. NMR spectra of above reported compounds:

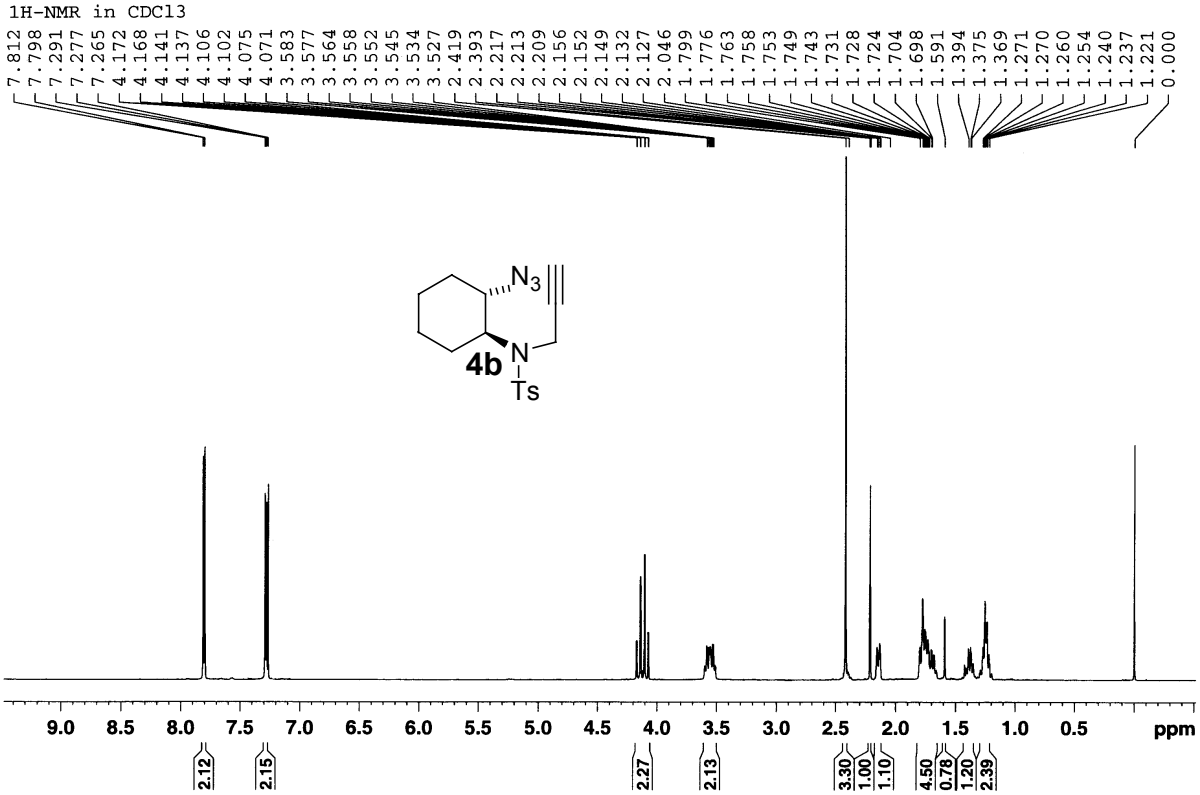
^{1}H NMR spectra of 4a (300 MHz):



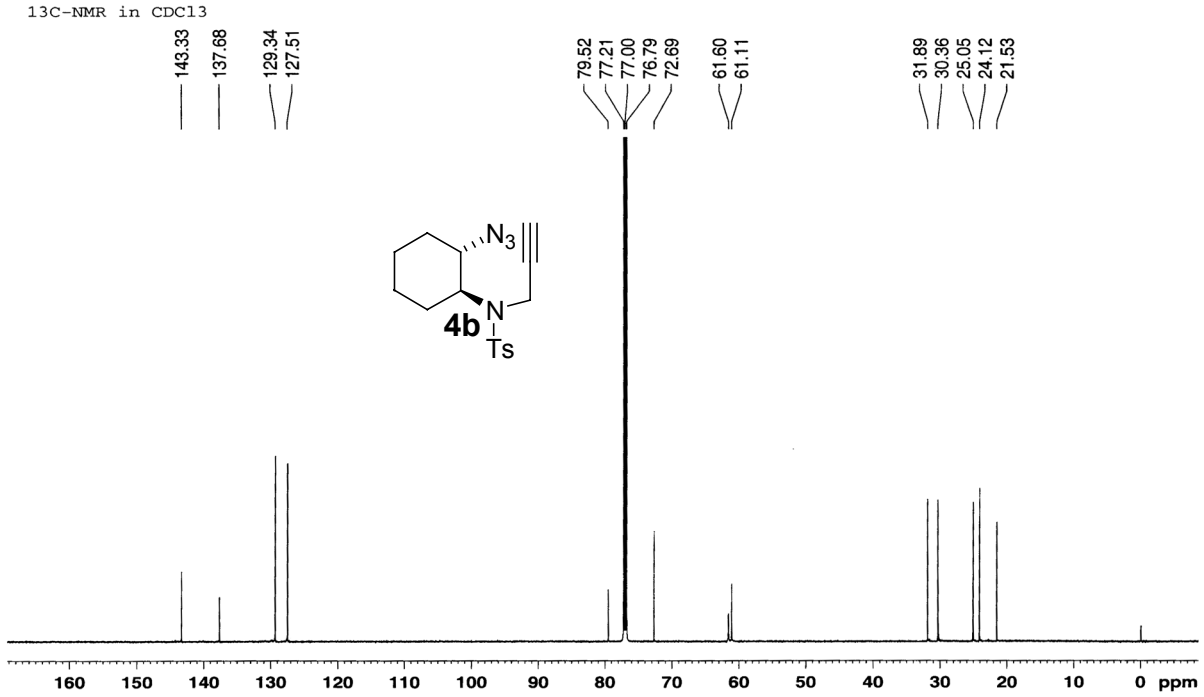
^{13}C NMR spectra of 4a (300 MHz):



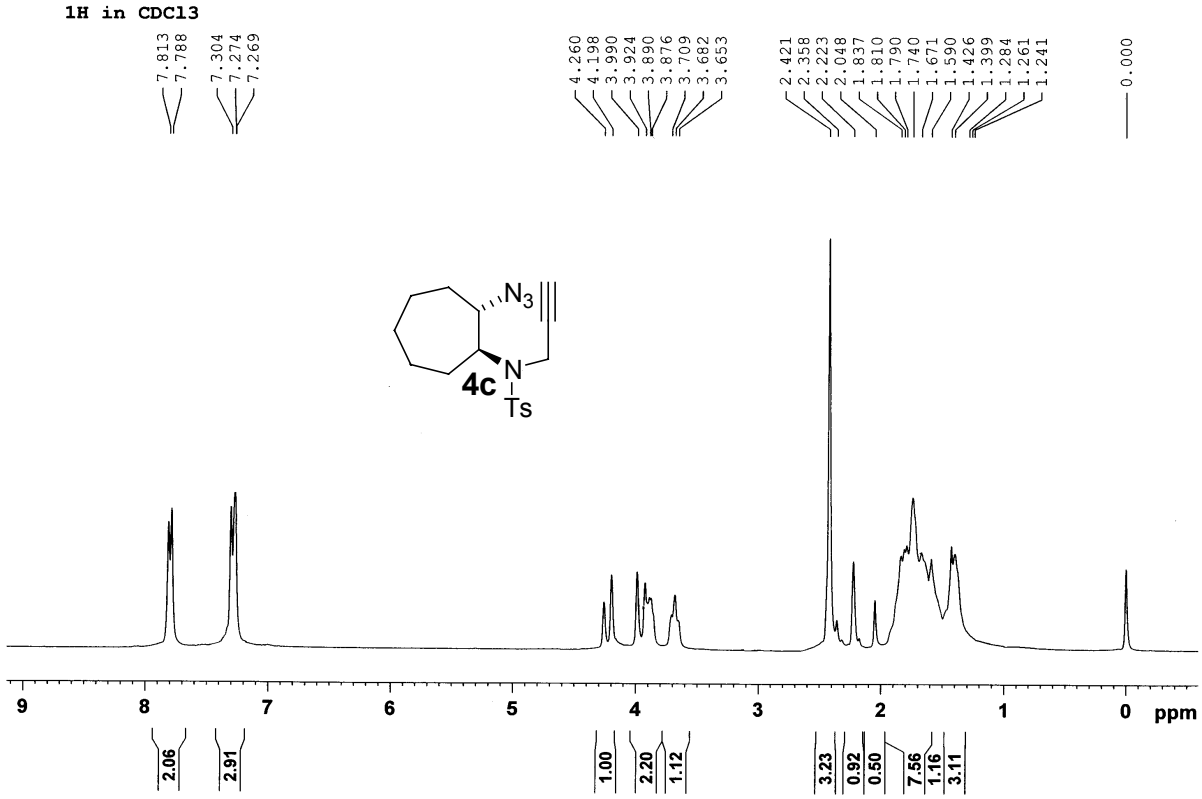
^{1}H NMR spectra of 4b (600 MHz):



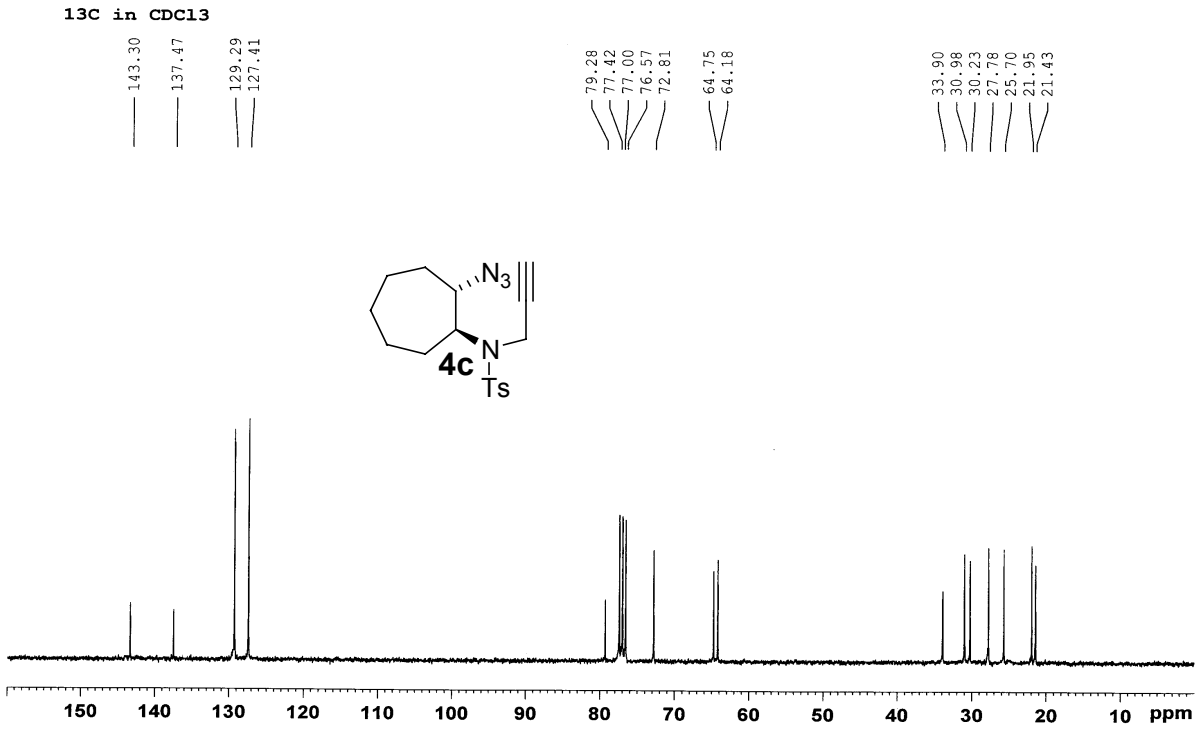
^{13}C NMR spectra of 4b (600 MHz):



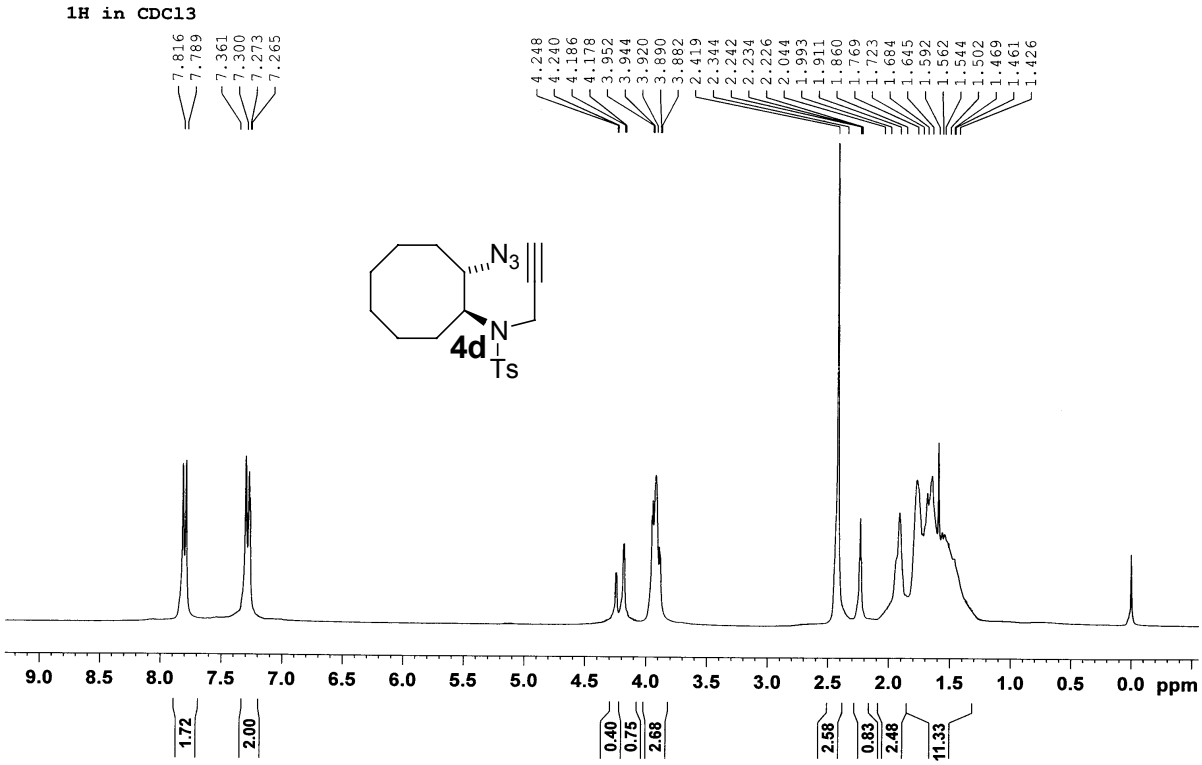
^{1}H NMR spectra of 4c (300 MHz):



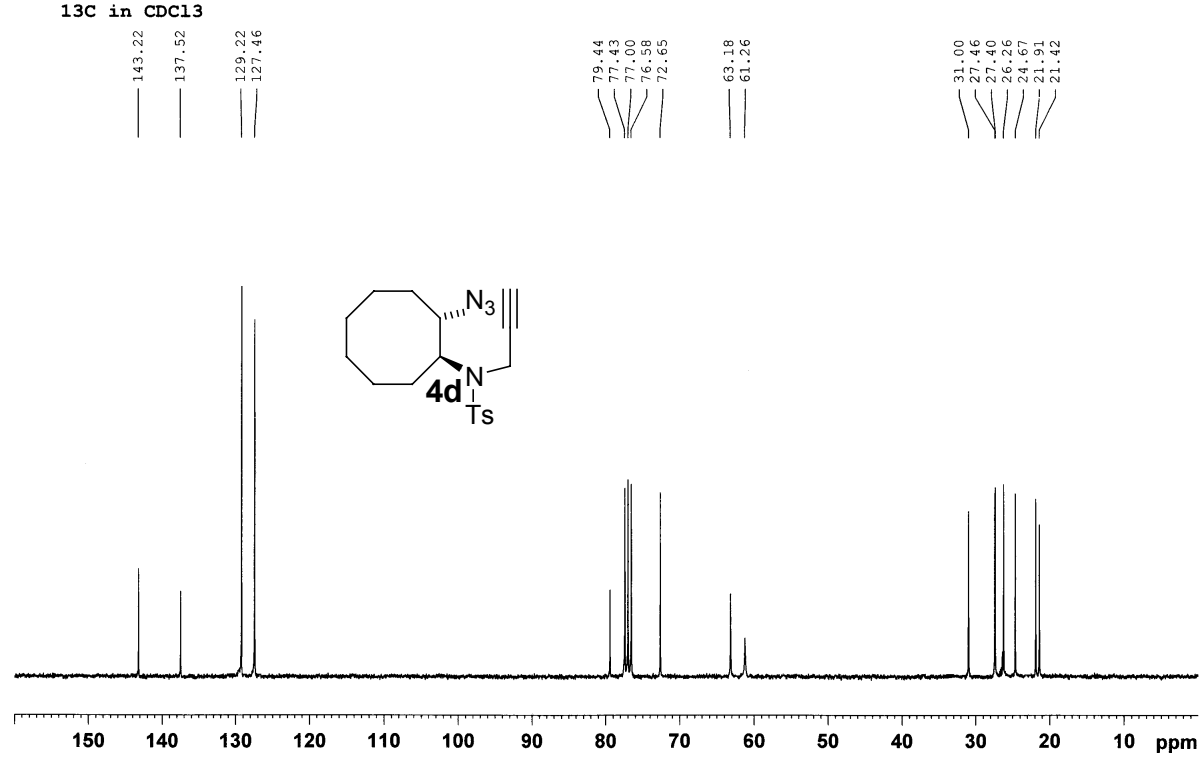
^{13}C NMR spectra of 4c (300 MHz):



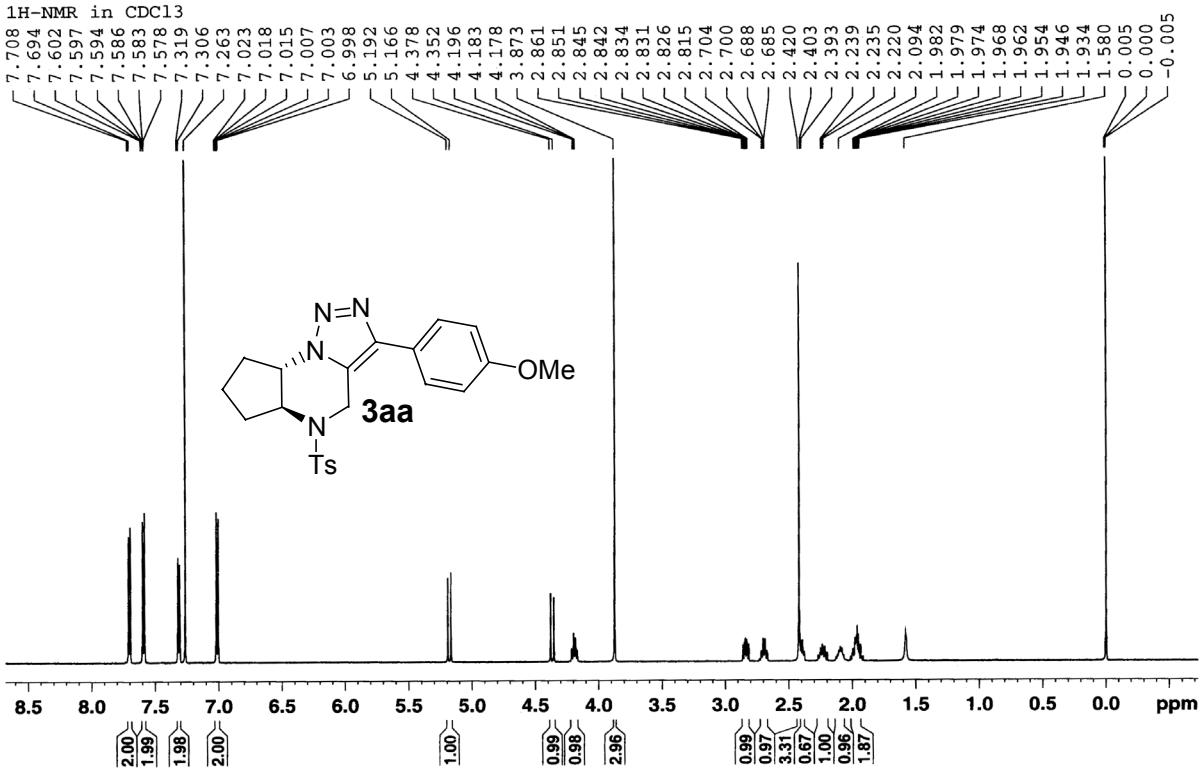
^{1}H NMR spectra of 4d (300 MHz):



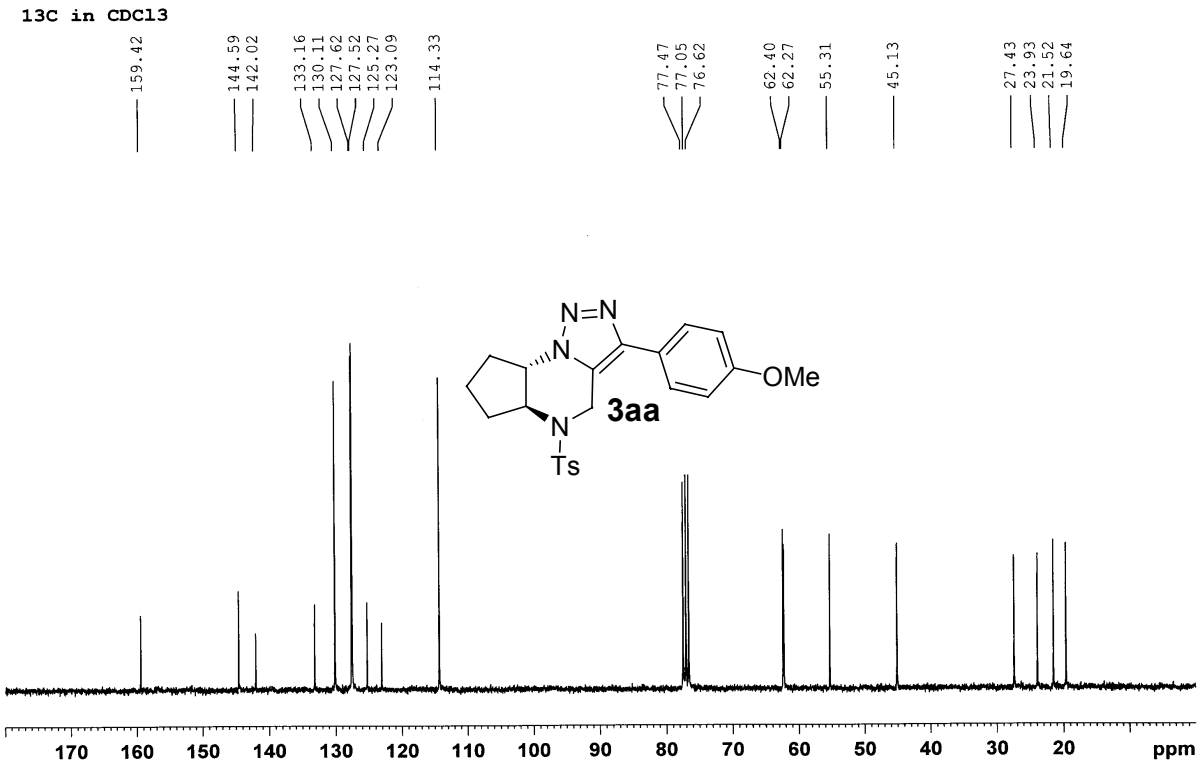
^{13}C NMR spectra of 4d (300 MHz):



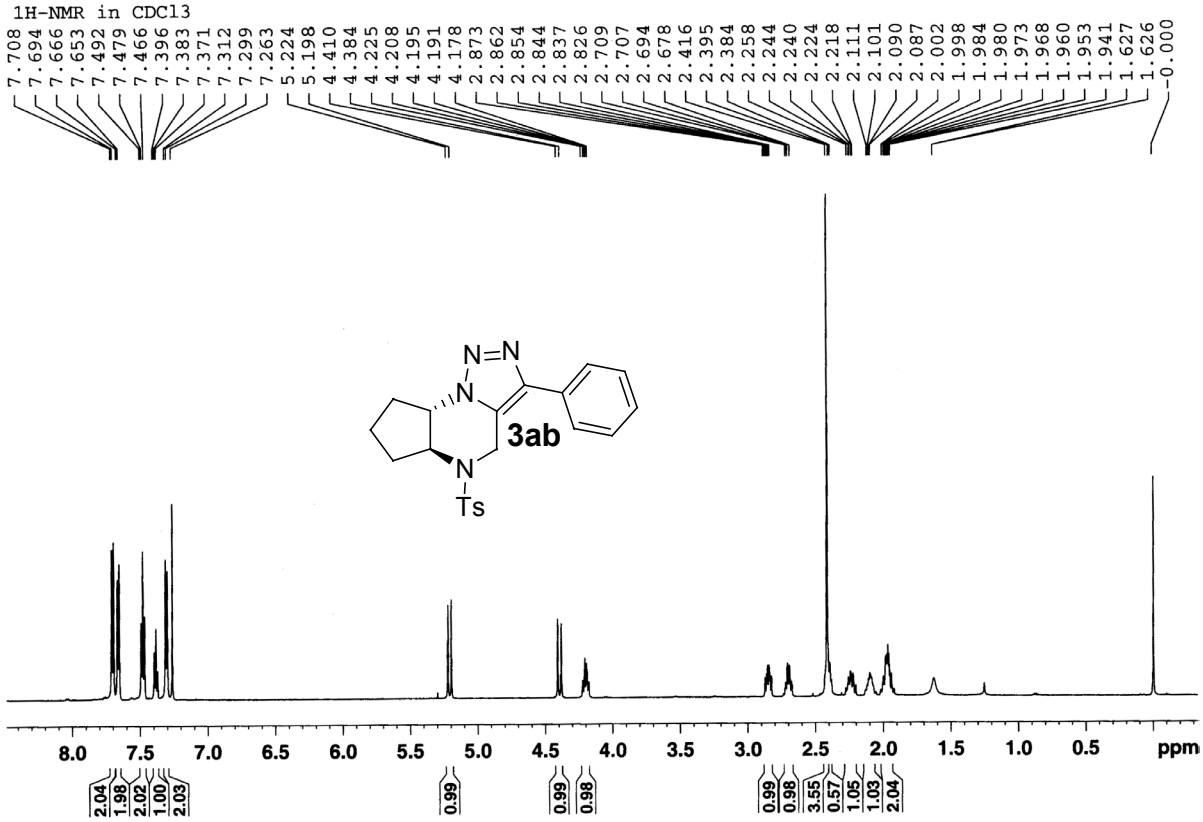
^{1}H NMR spectra of 3aa (600 MHz):



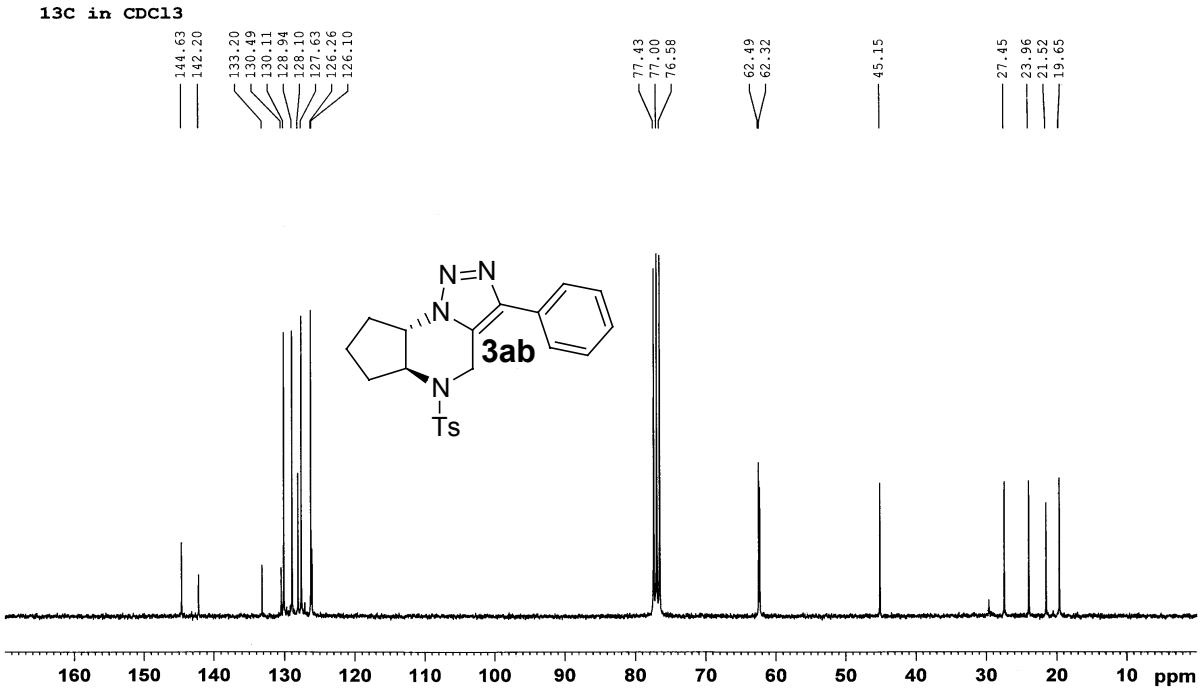
^{13}C NMR spectra of 3aa (300 MHz):



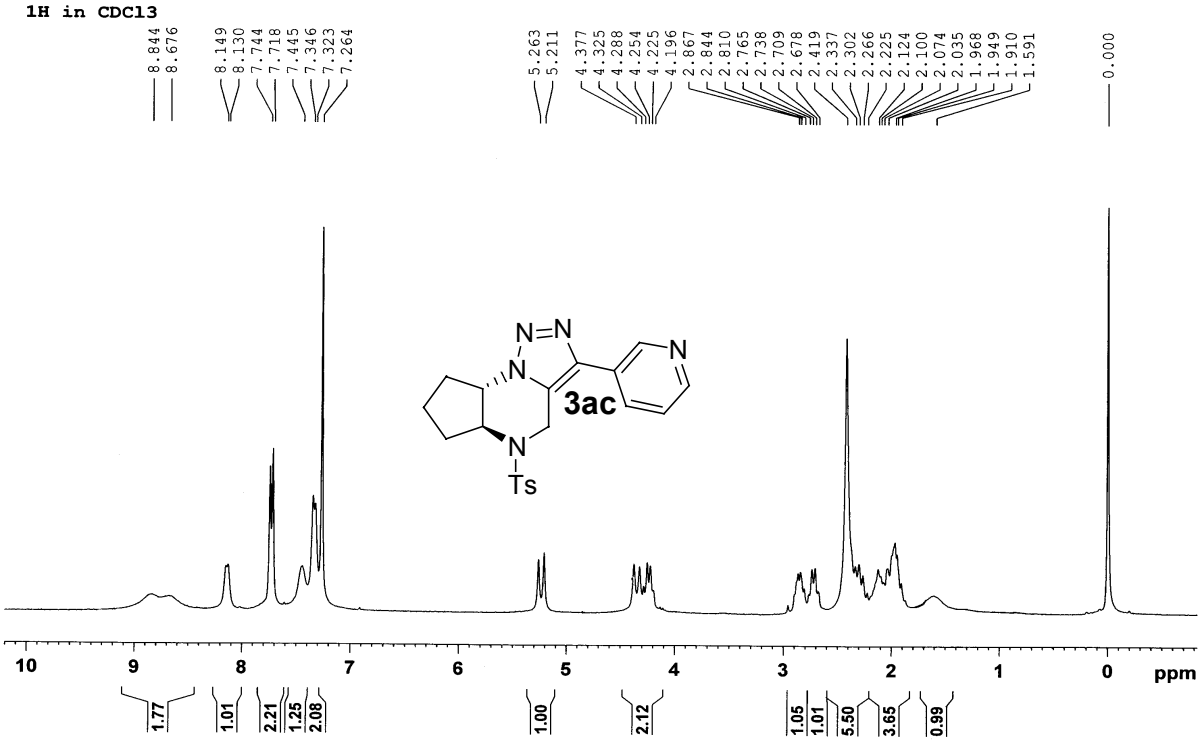
^{1}H NMR spectra of 3ab (600 MHz):



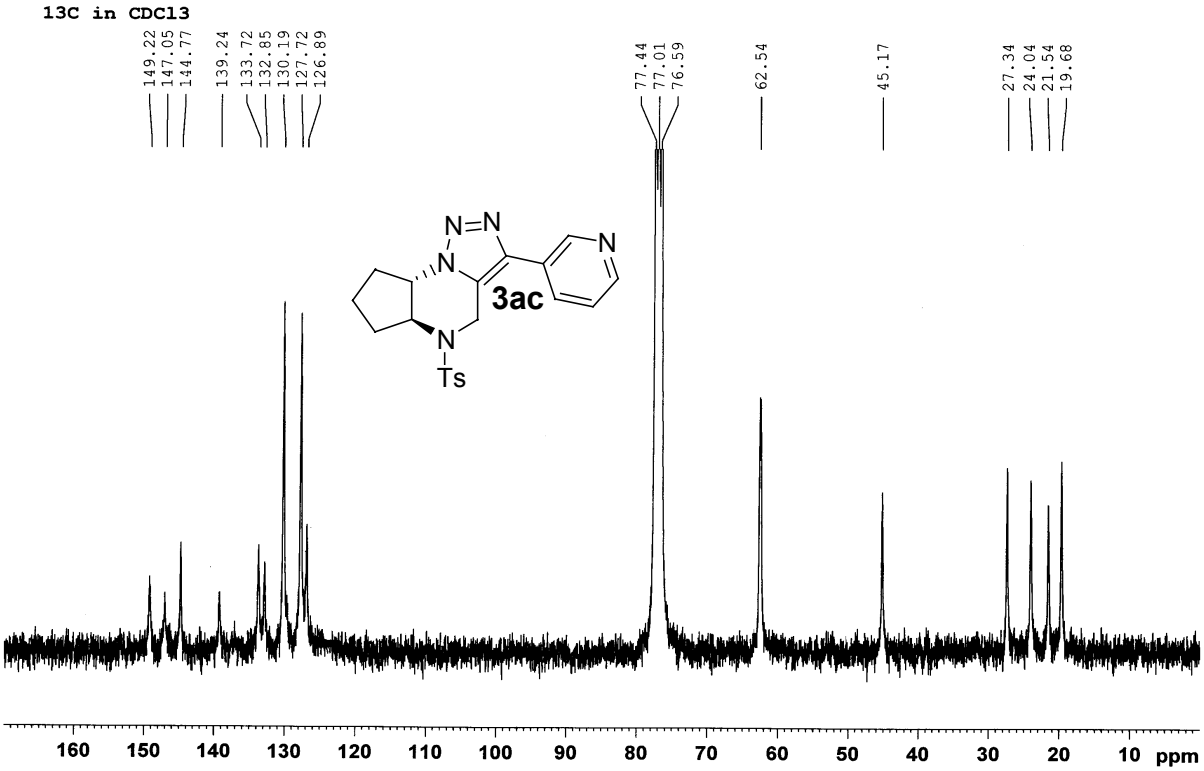
^{13}C NMR spectra of 3ab (300 MHz):



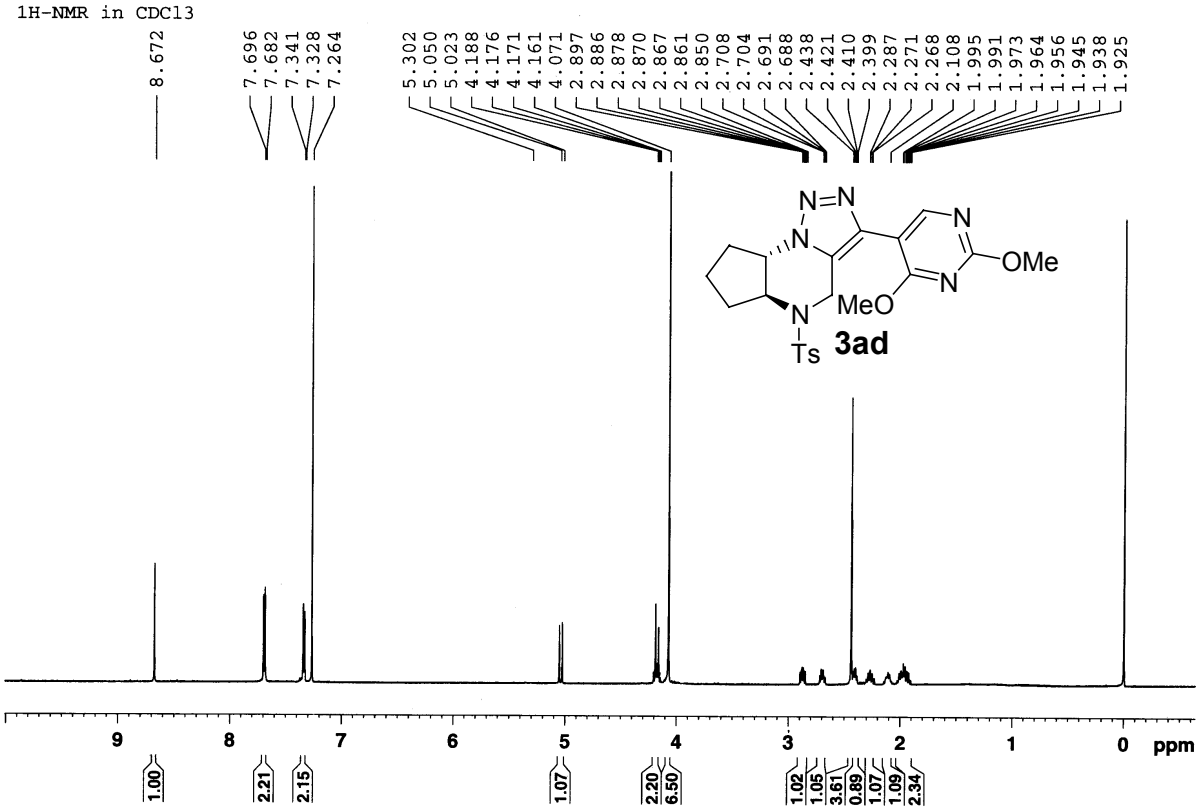
^{1}H NMR spectra of 3ac (300 MHz):



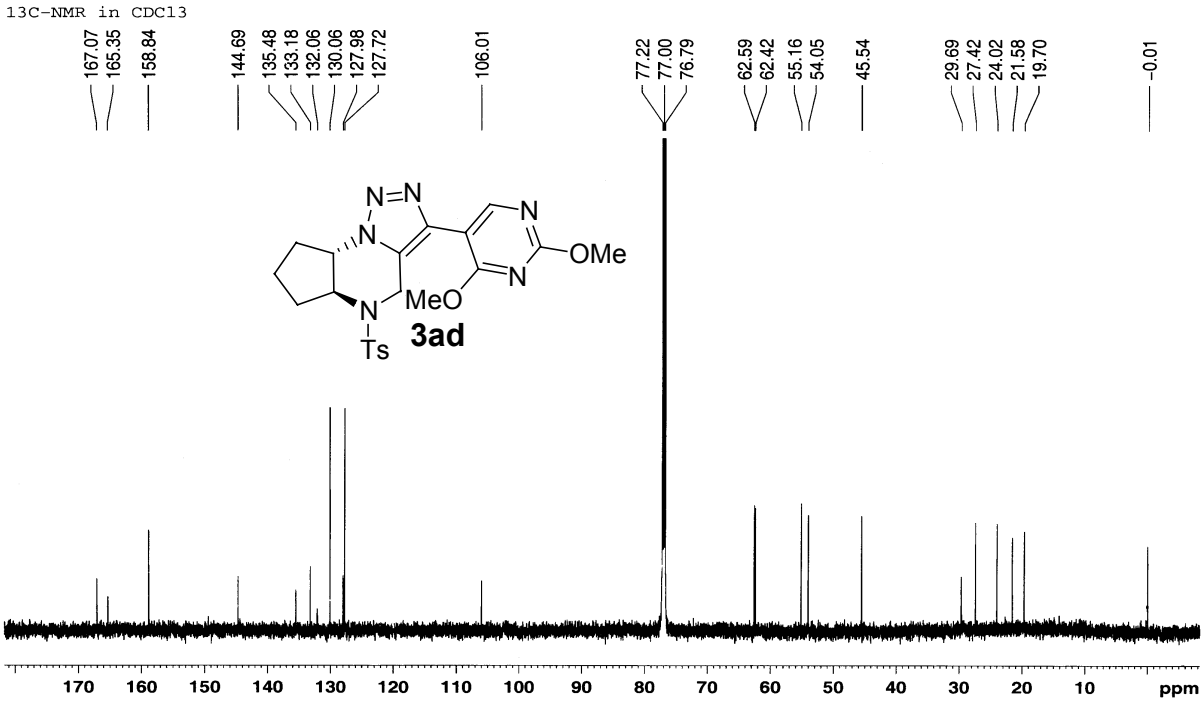
^{13}C NMR spectra of 3ac (300 MHz):



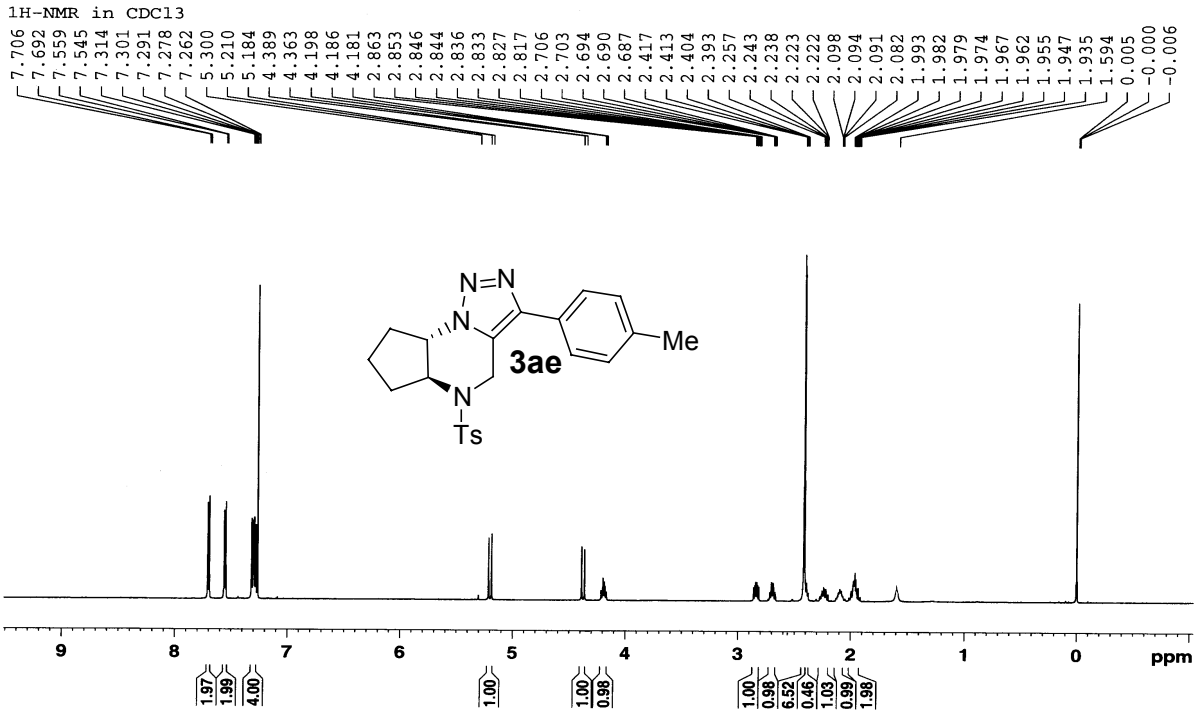
^{1}H NMR spectra of 3ad (600 MHz):



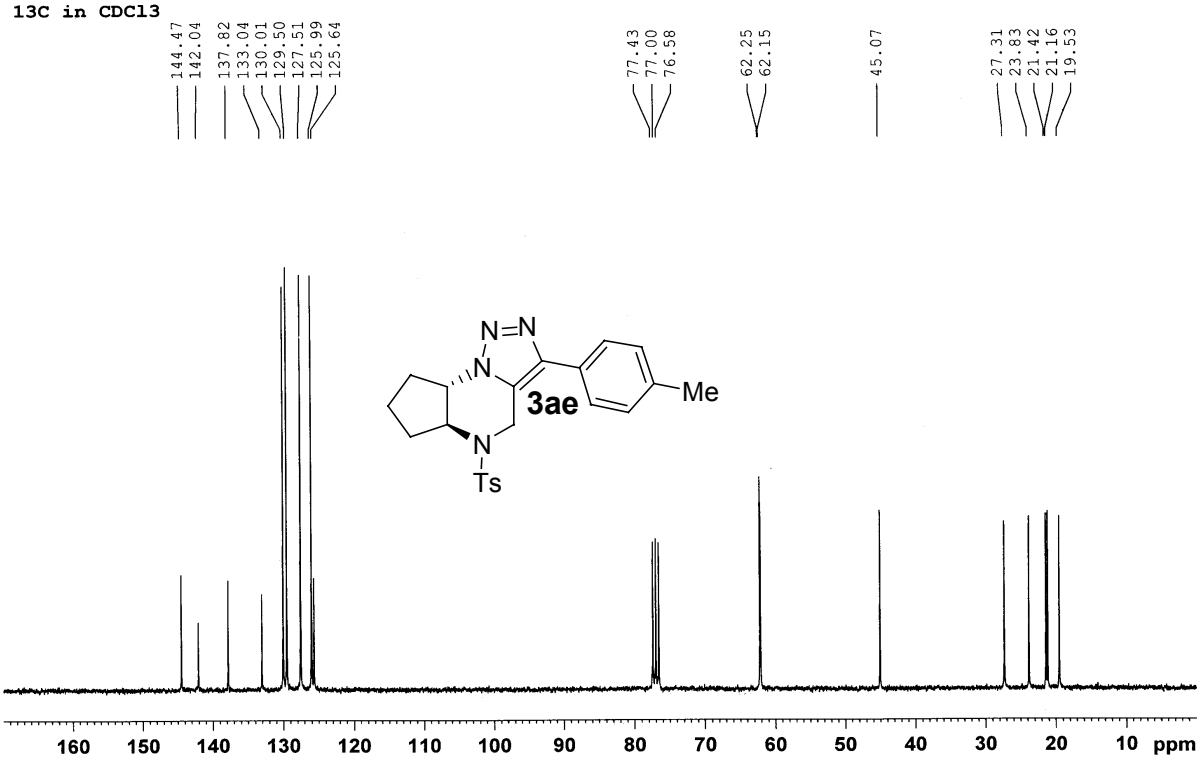
^{13}C NMR spectra of 3ad (600 MHz):



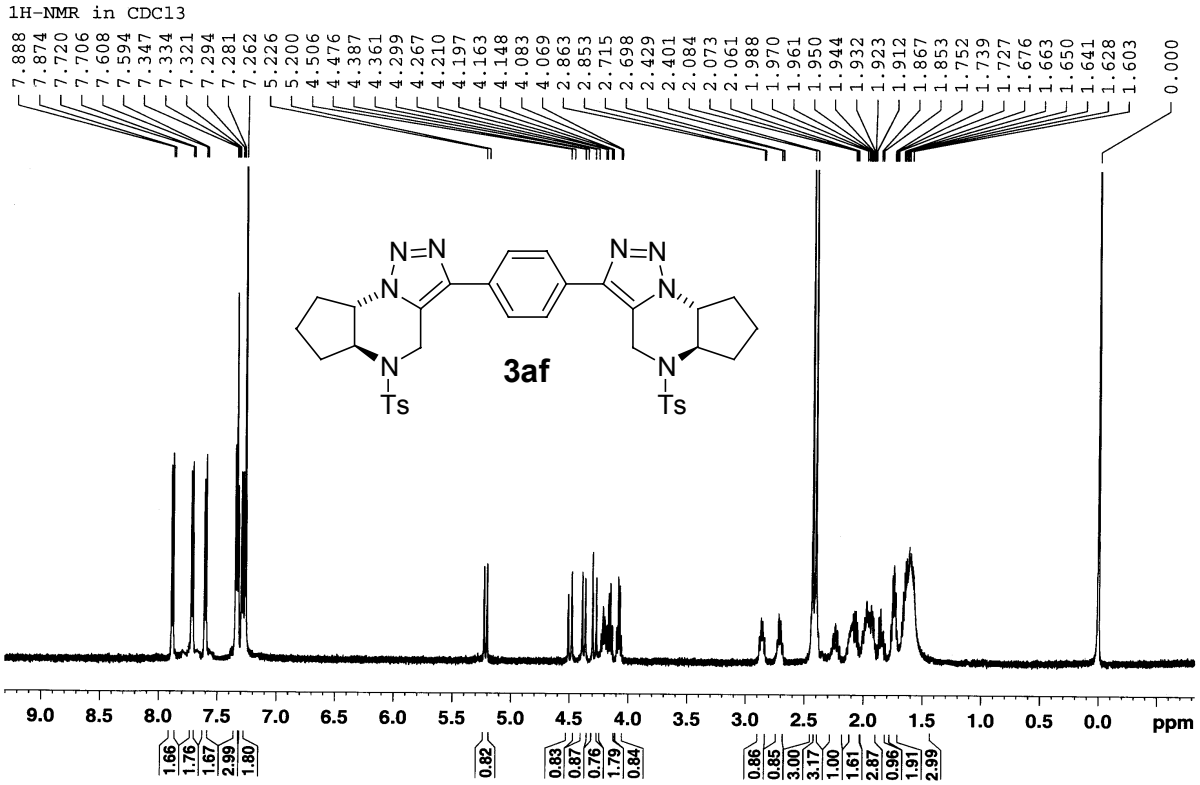
^{1}H NMR spectra of 3ae (600 MHz):



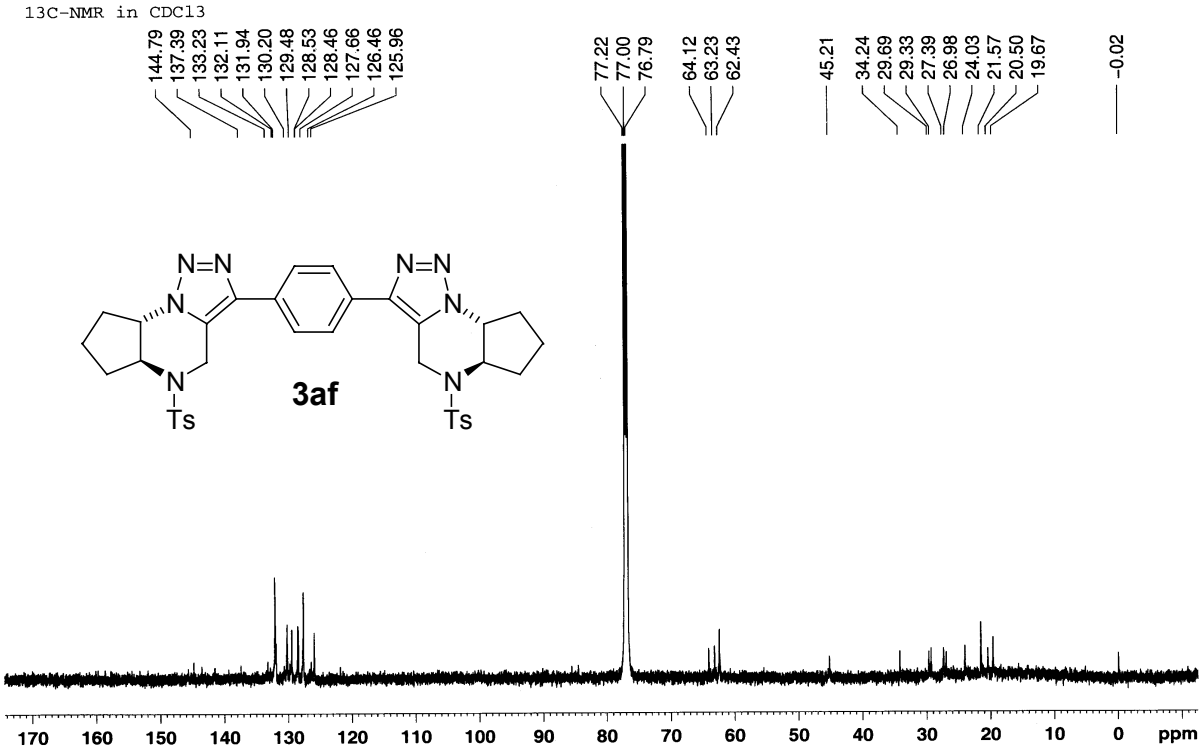
^{13}C NMR spectra of 3ae (300 MHz):



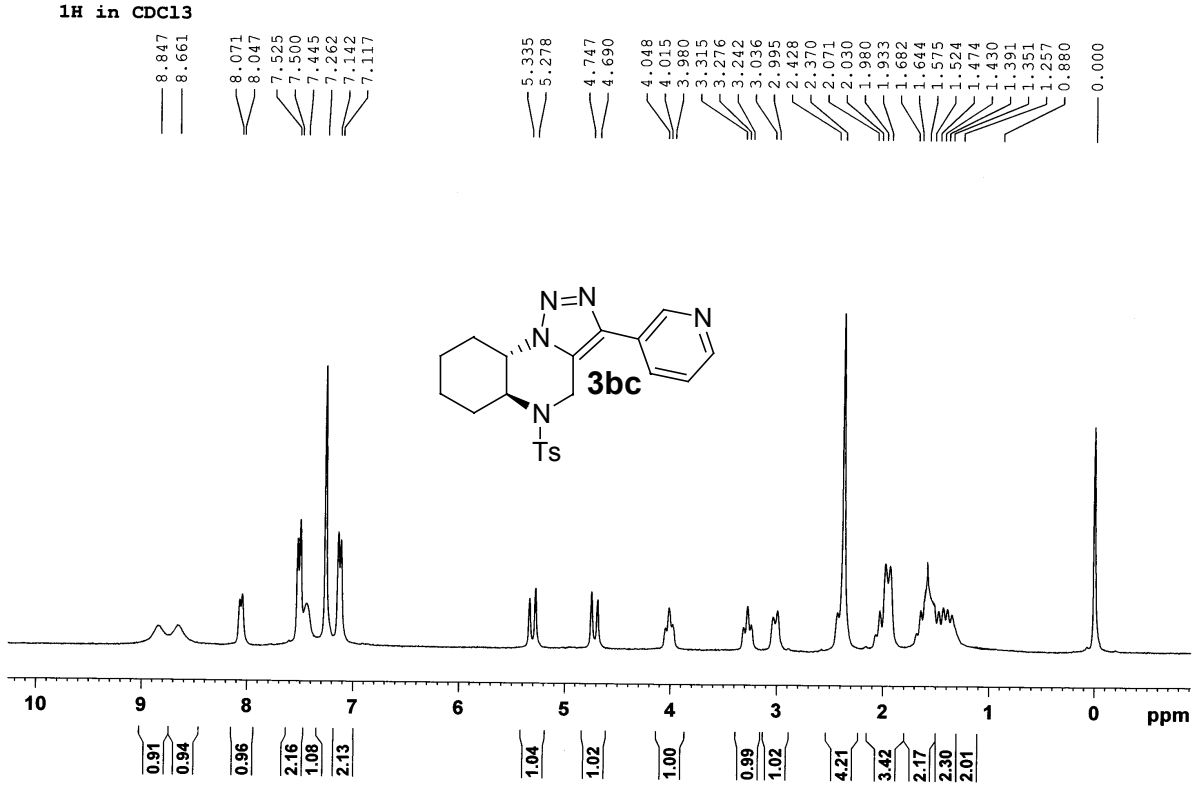
^{1}H NMR spectra of 3af (600 MHz):



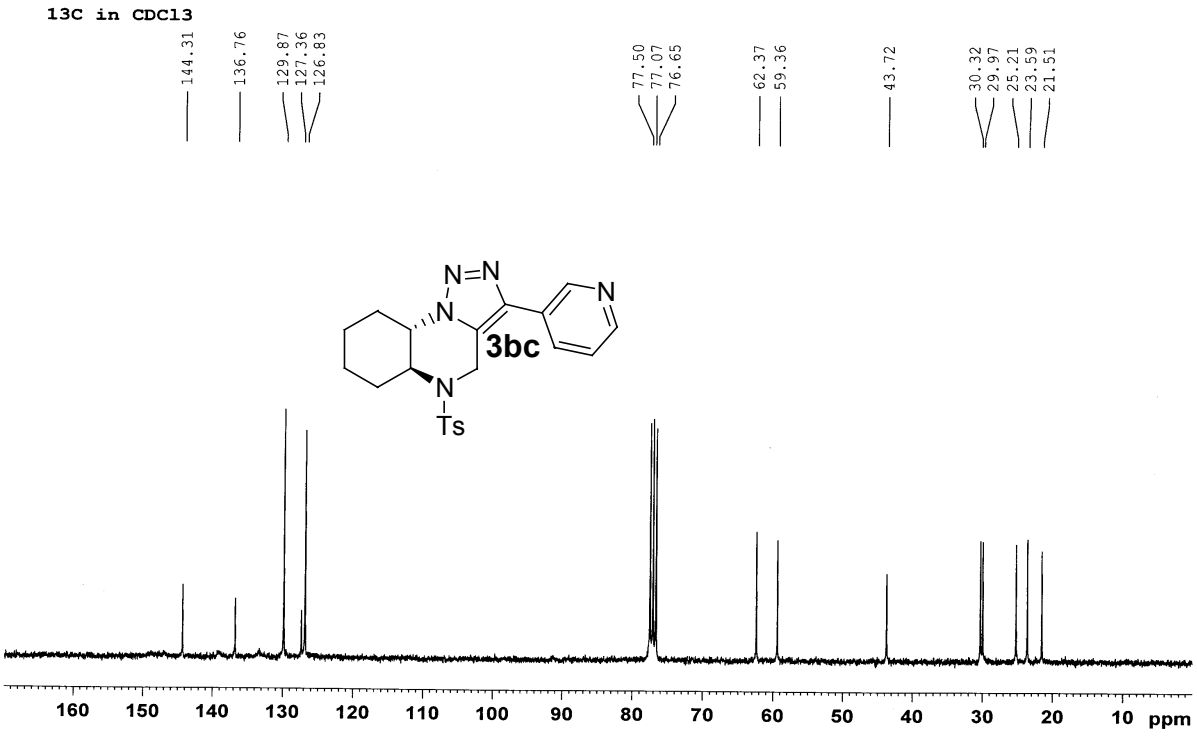
^{13}C NMR spectra of 3af (600 MHz):



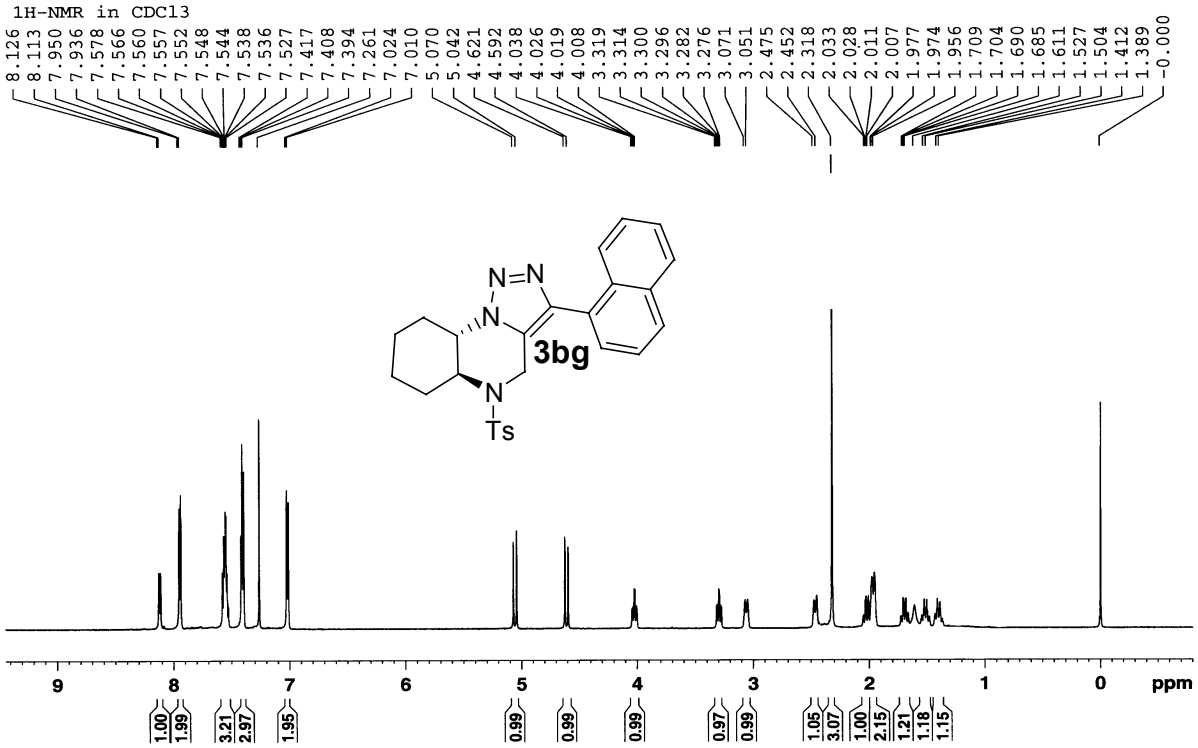
^{1}H NMR spectra of 3bc (300 MHz):



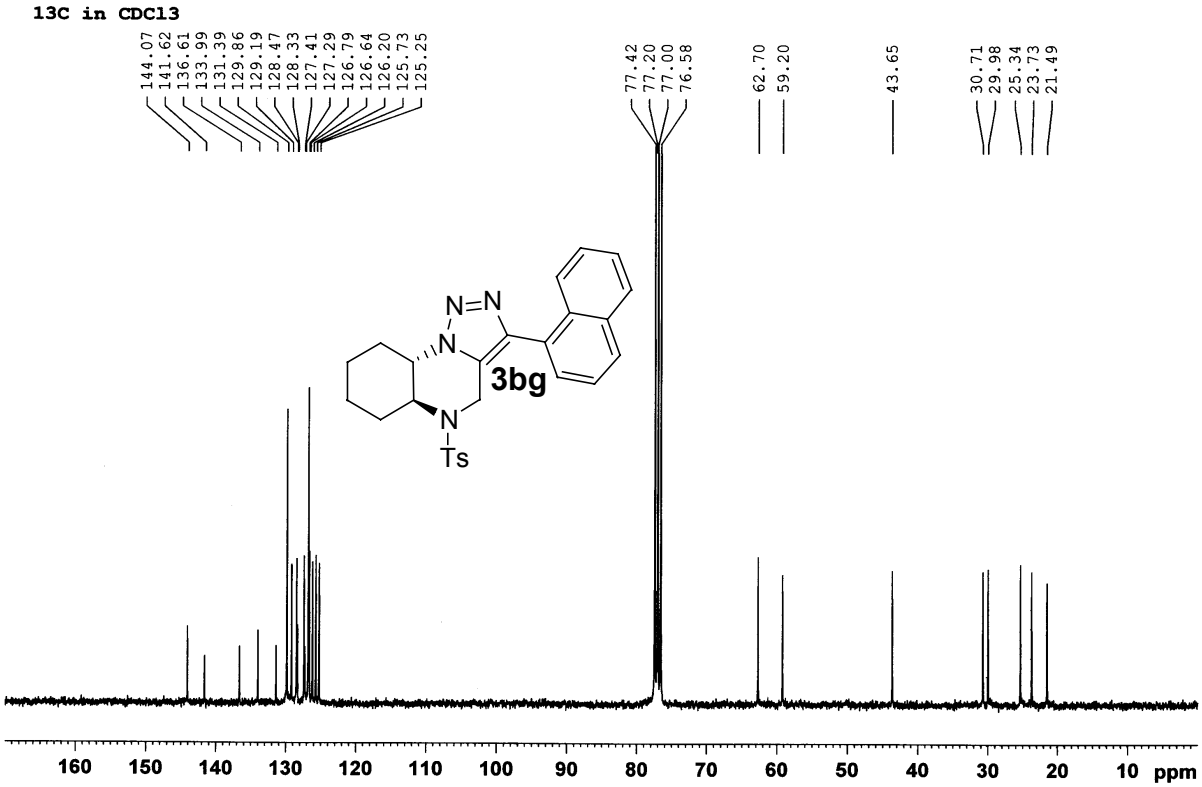
^{13}C NMR spectra of 3bc (300 MHz):



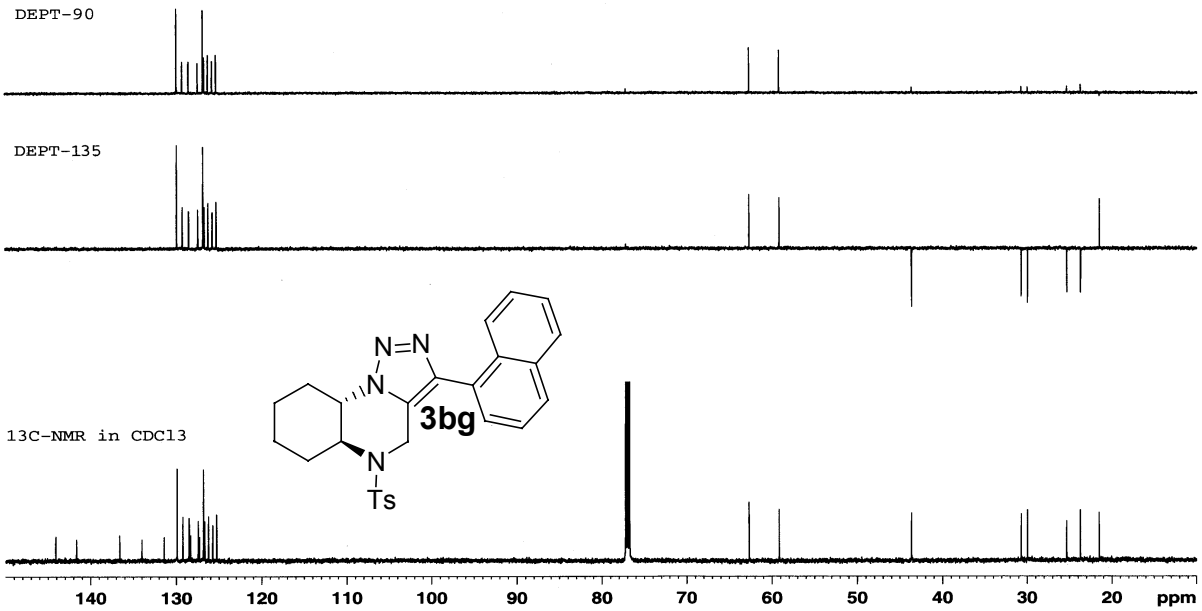
^{1}H NMR spectra of 3bg (600 MHz):



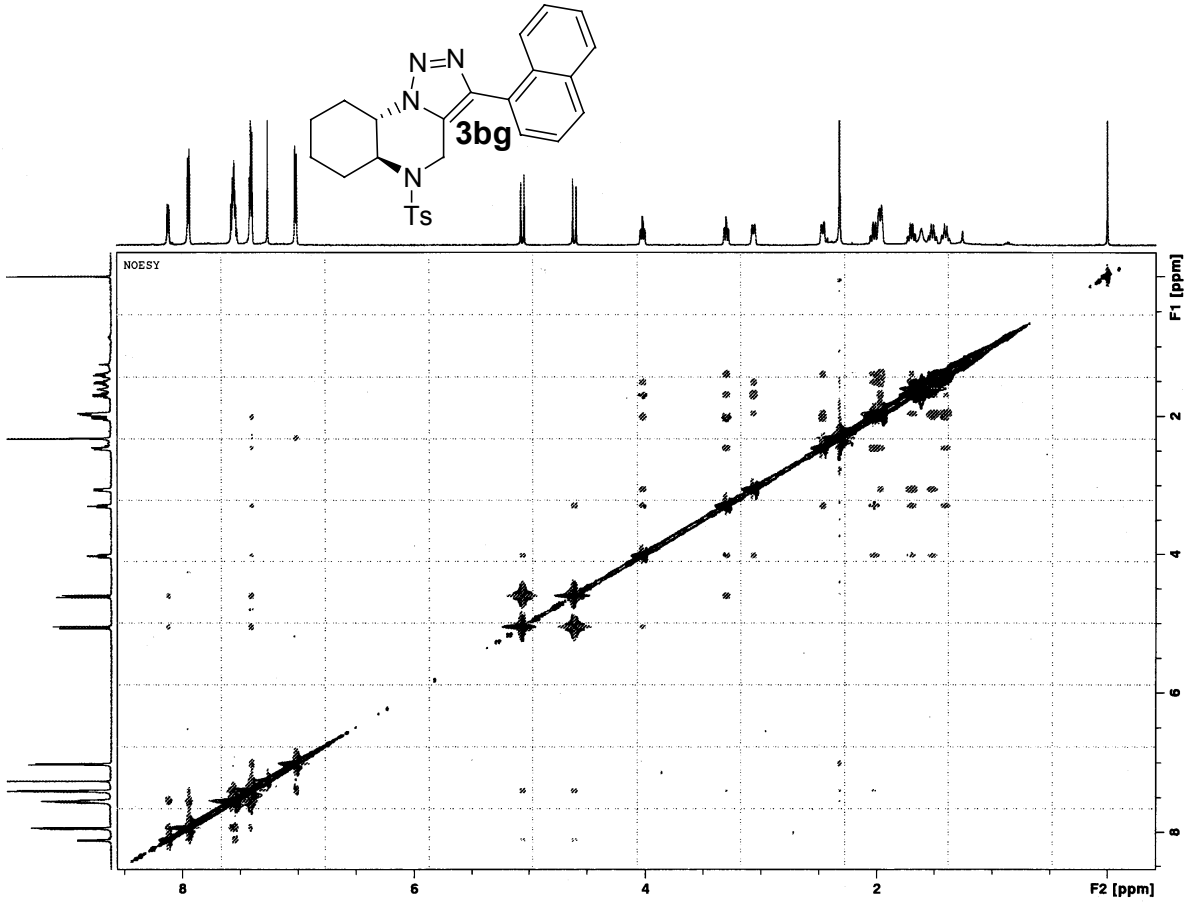
^{13}C NMR spectra of 3bg (300 MHz):



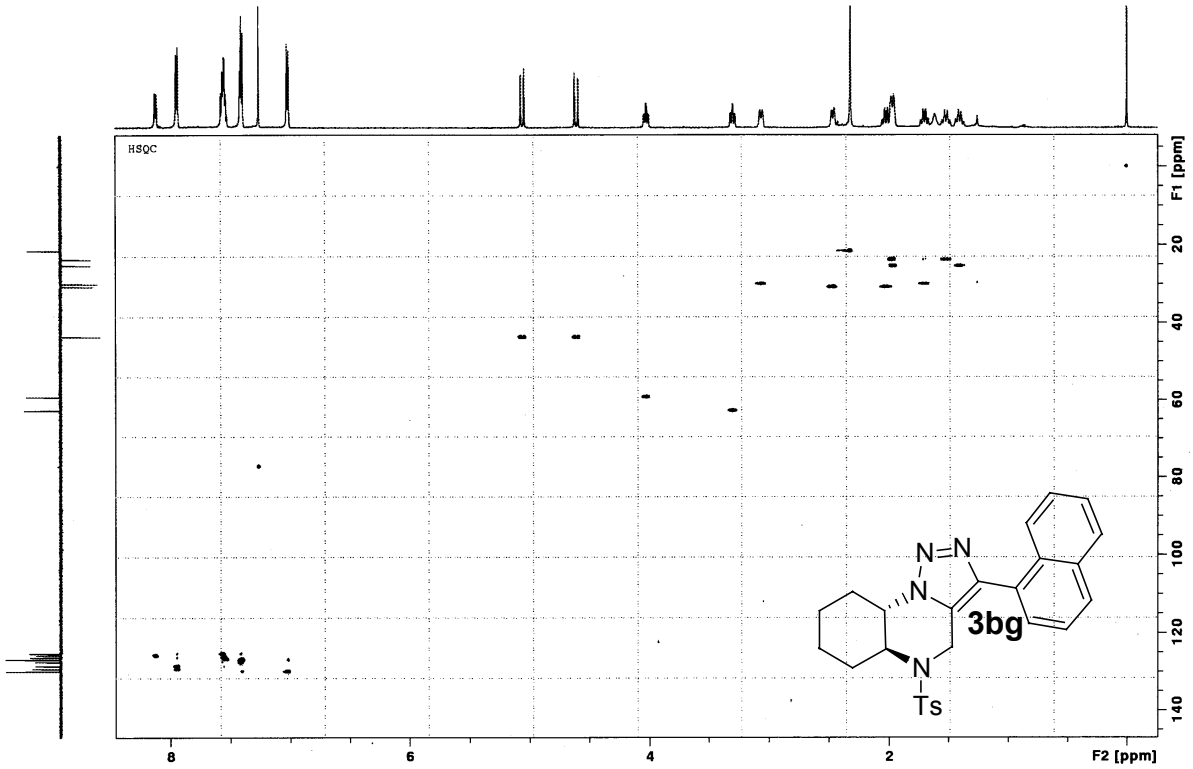
DEPT of 3bg (300 MHz):



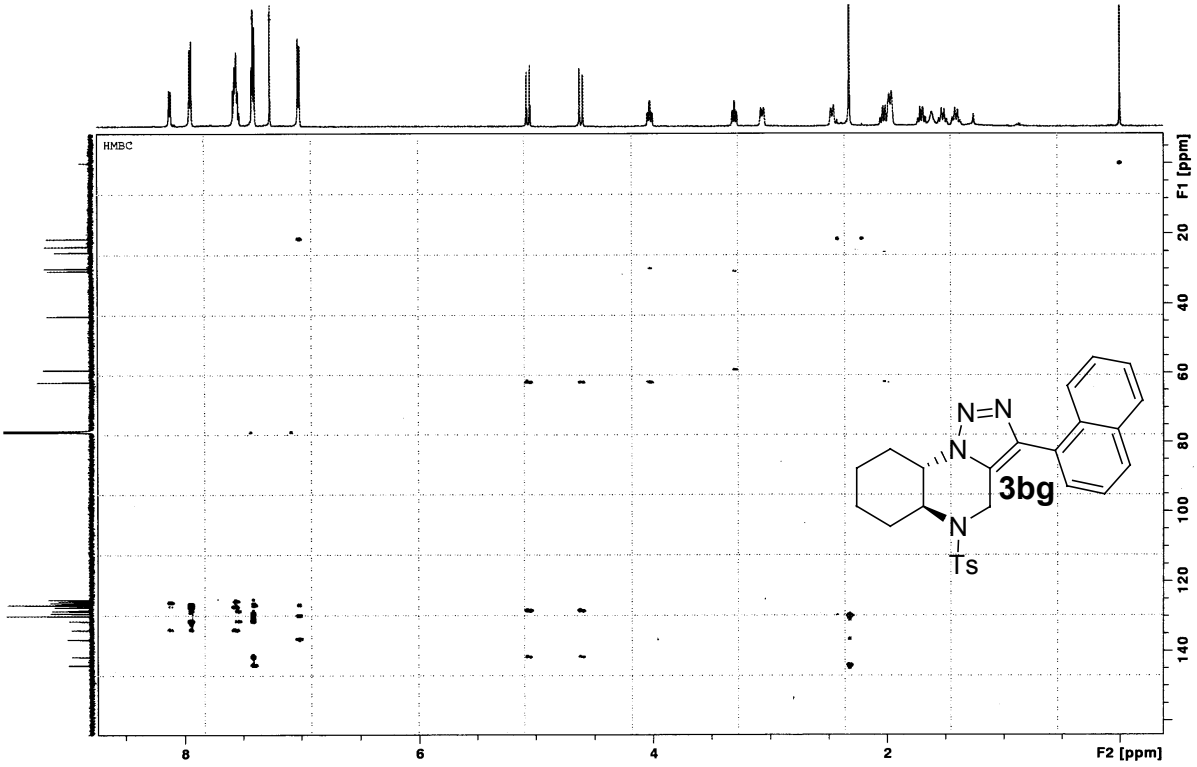
NOESY of 3bg (600 MHz):



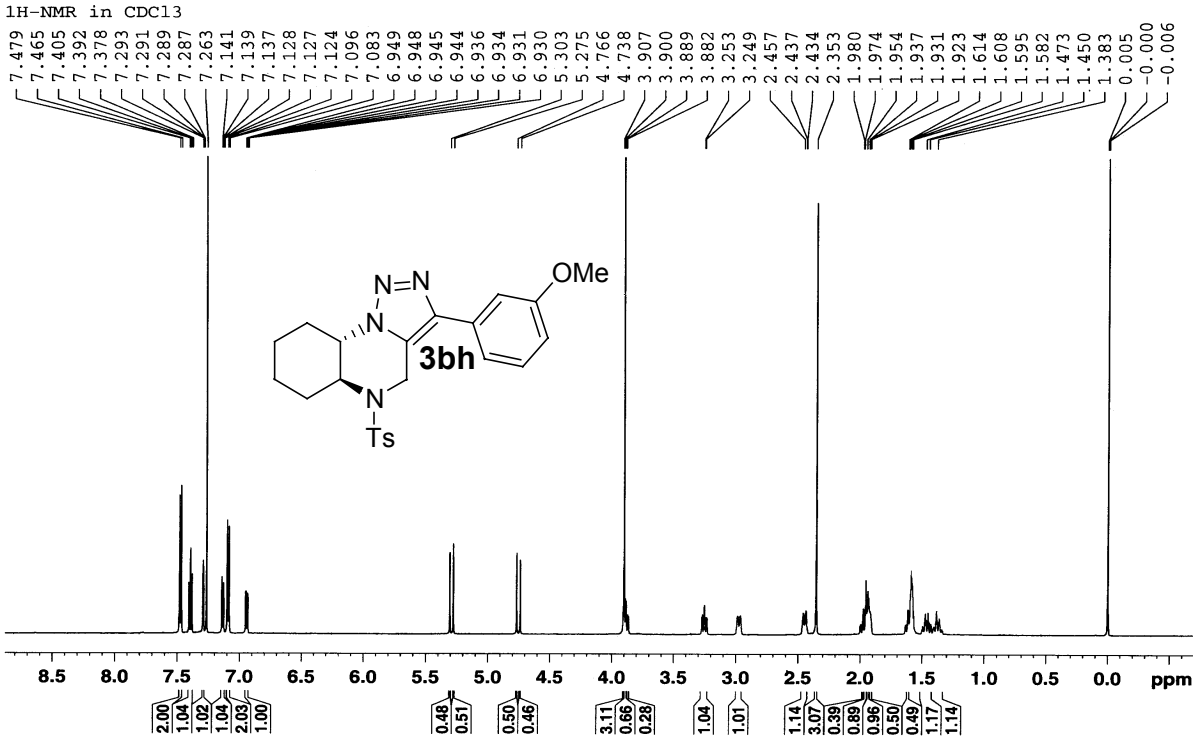
HSQC of 3bg (600 MHz):



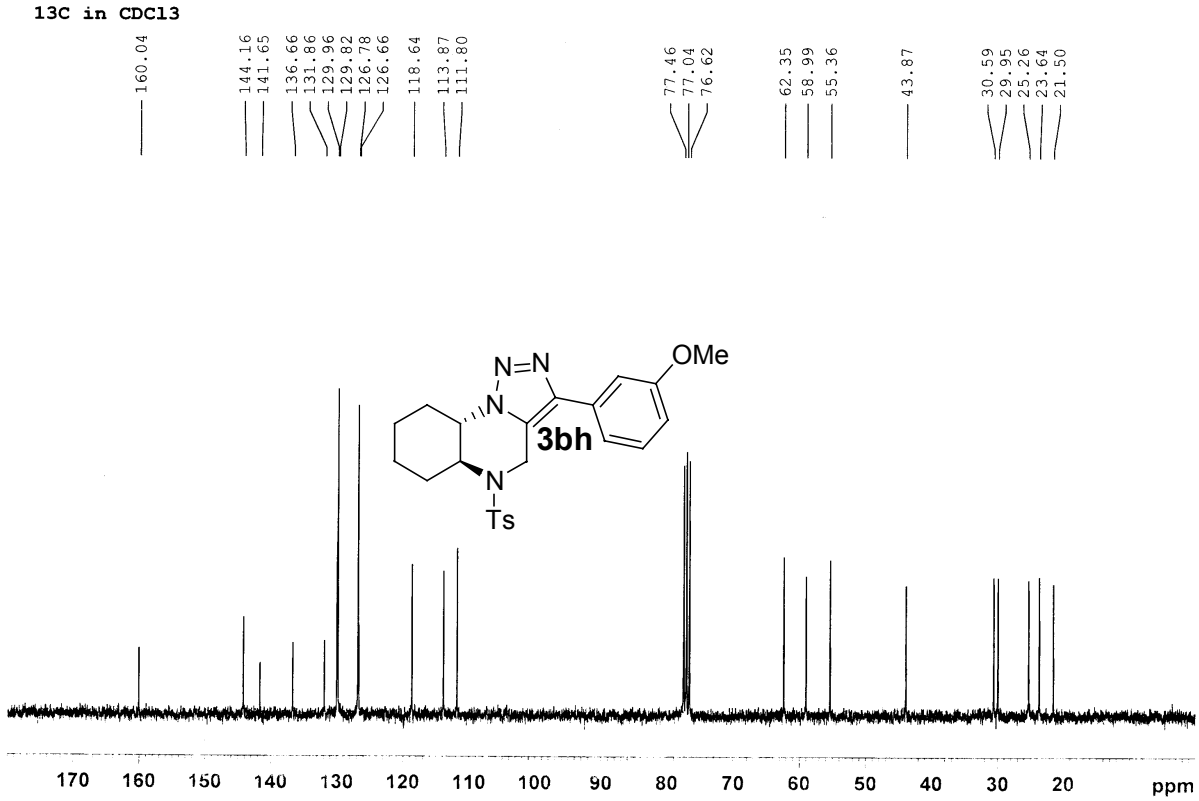
HMBC of 3bg (600 MHz):



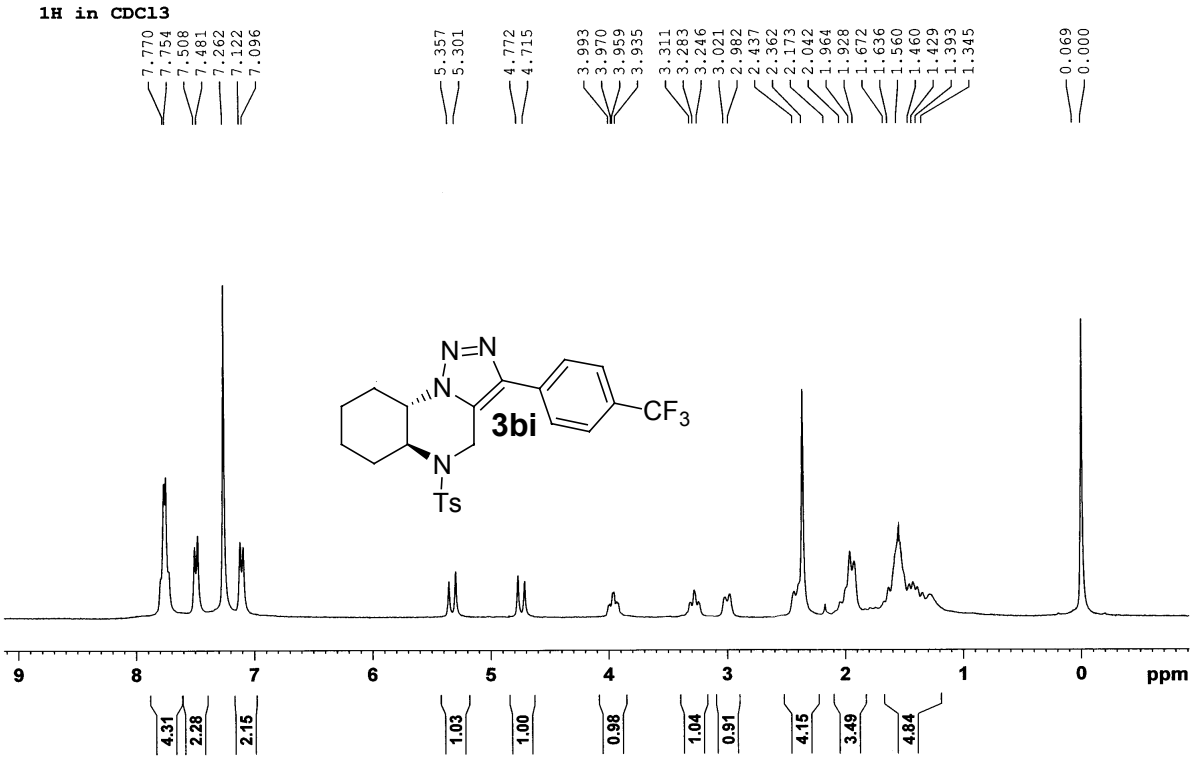
^{1}H NMR spectra of 3bh (600 MHz):



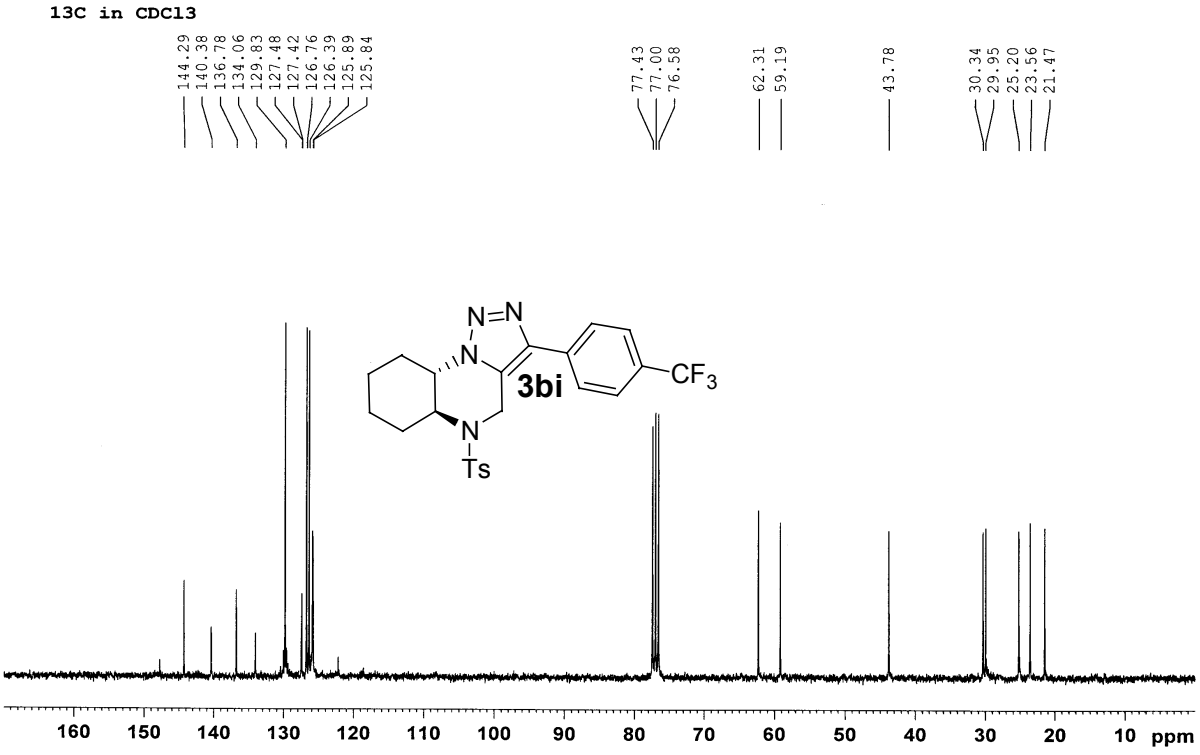
^{13}C NMR spectra of 4bh (300 MHz):



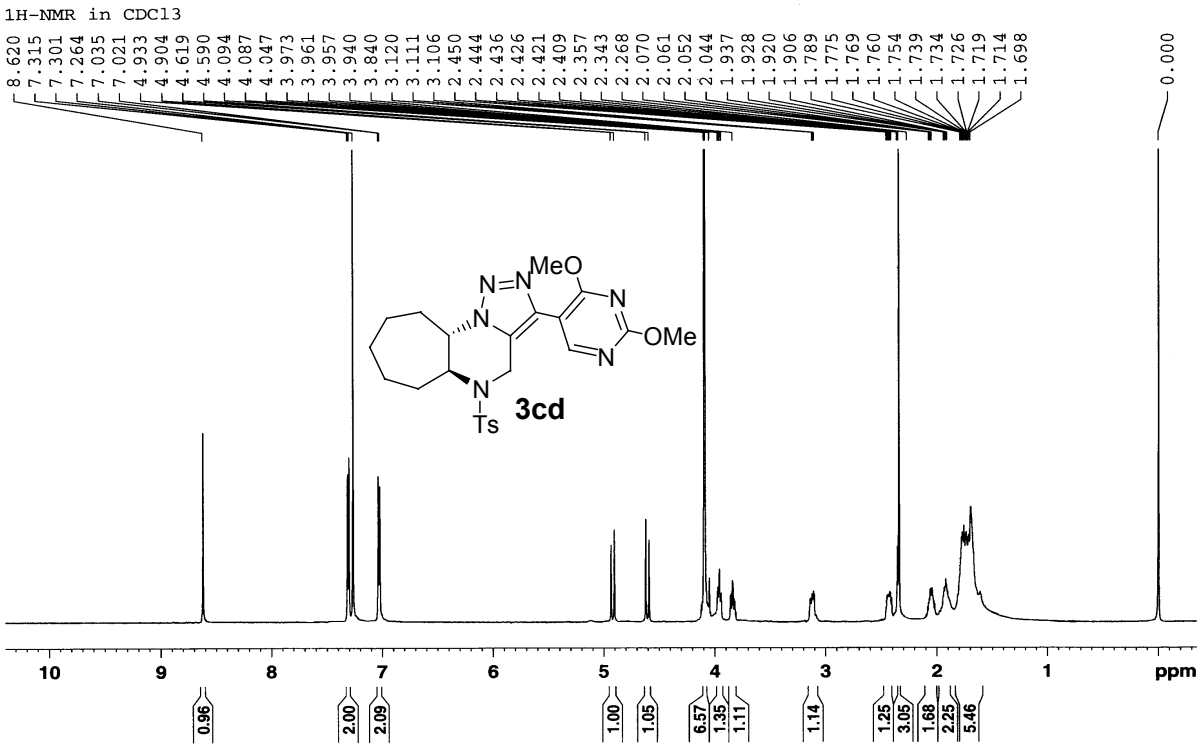
^{1}H NMR spectra of 4bi (300 MHz):



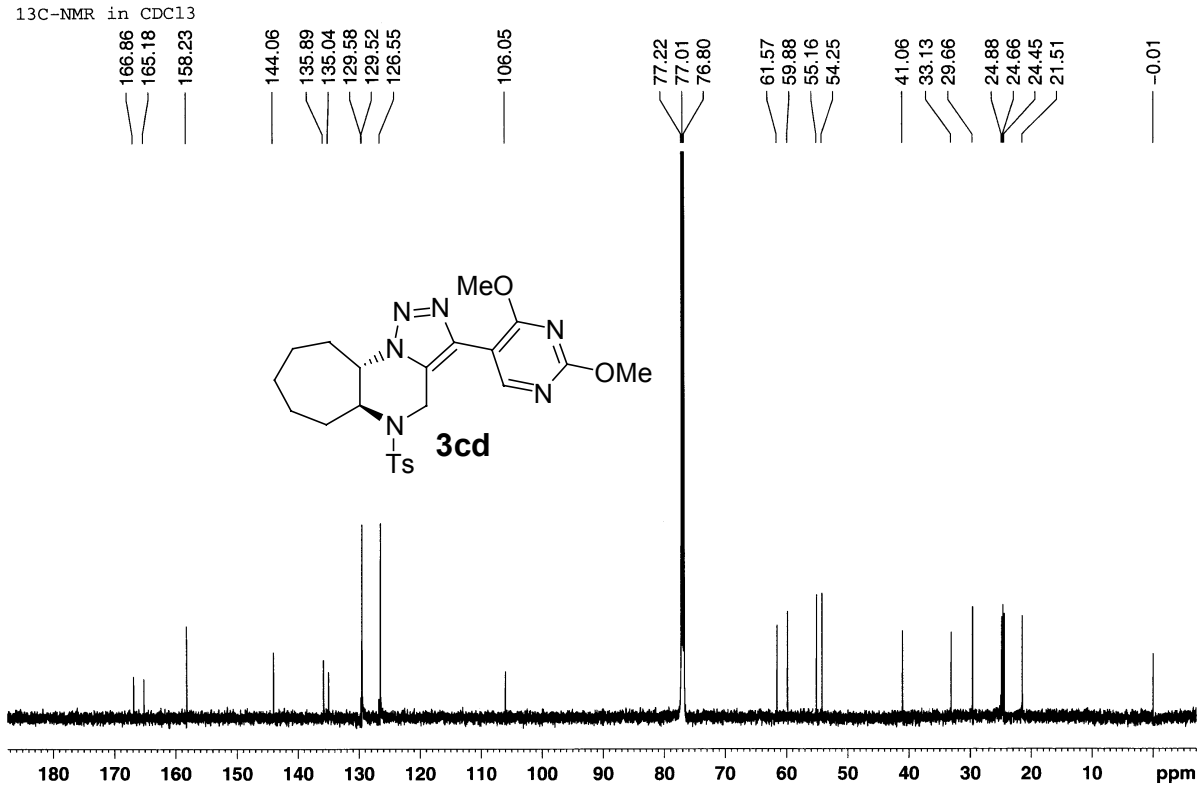
^{13}C NMR spectra of 3bi (300 MHz):



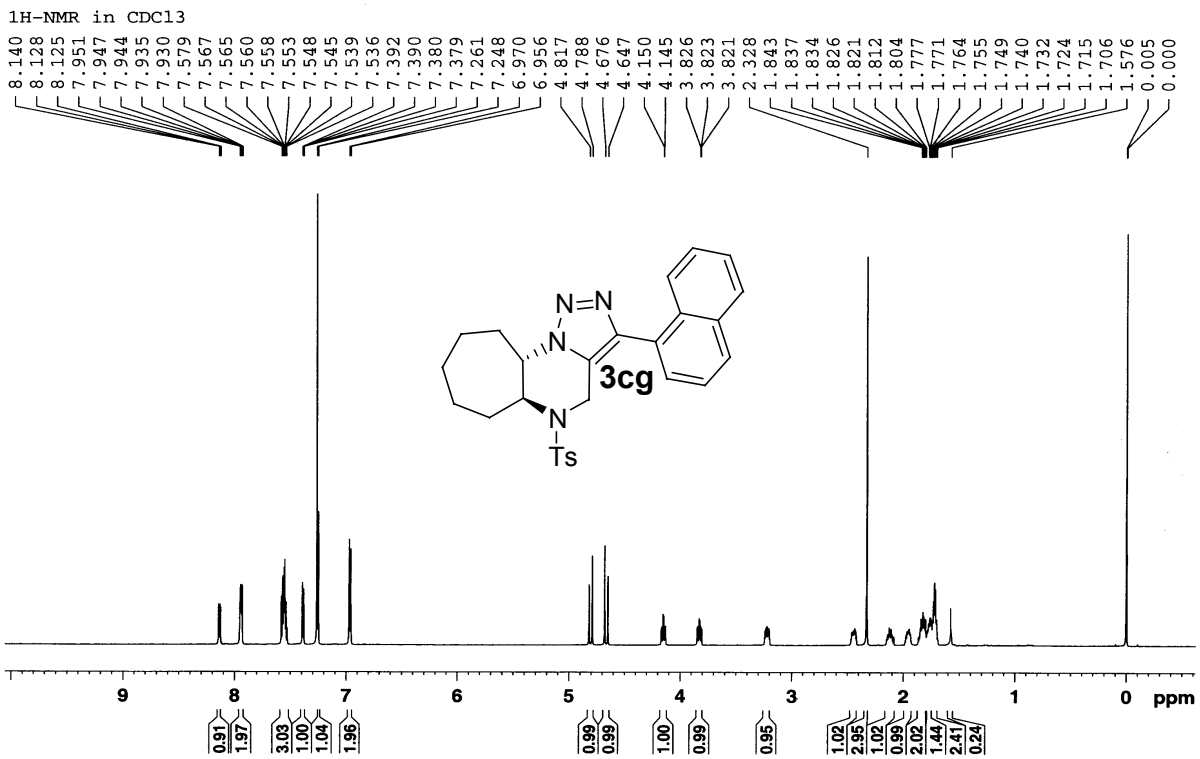
^{1}H NMR spectra of 3cd (600 MHz):



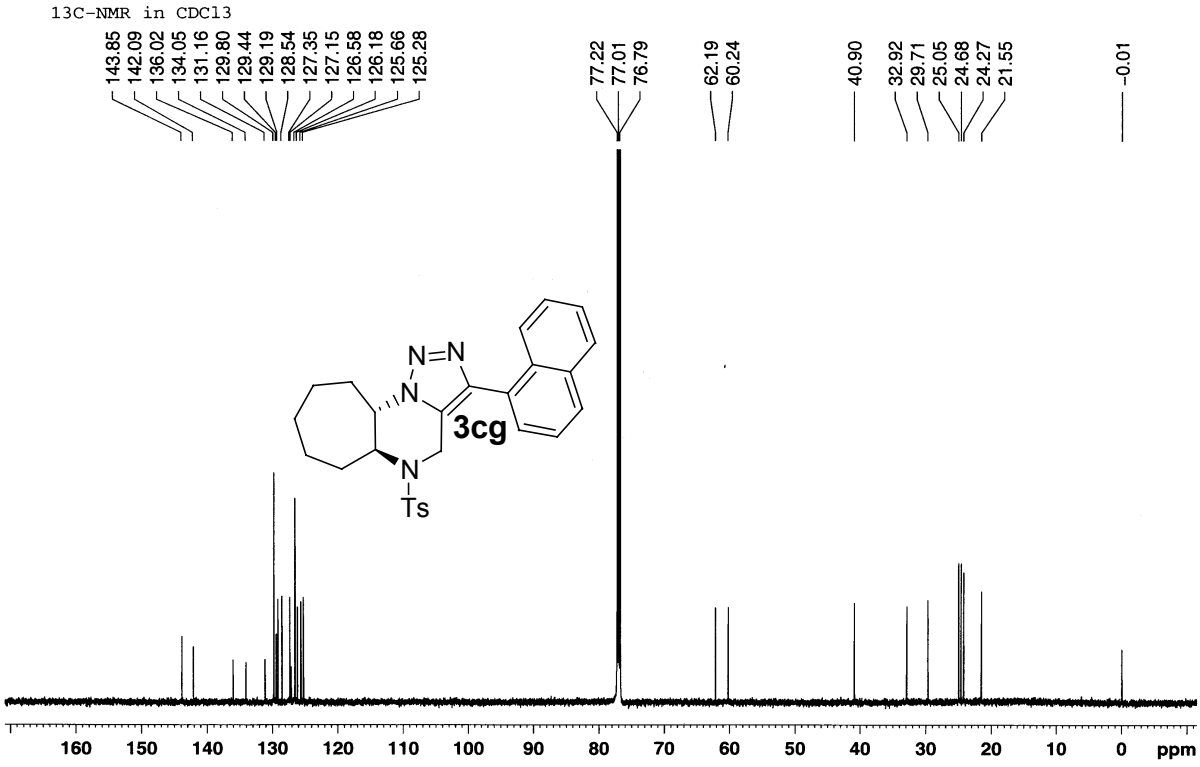
^{13}C NMR spectra of 3cd (600 MHz):



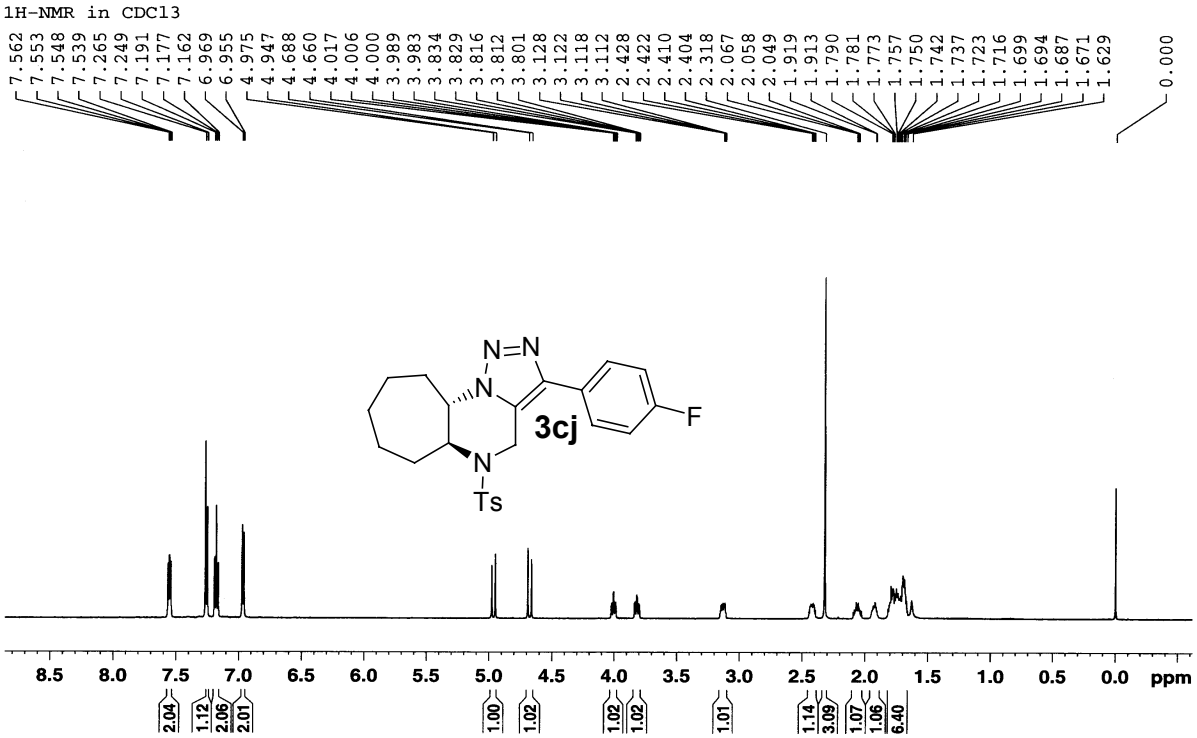
^{1}H NMR spectra of 3cg (600 MHz):



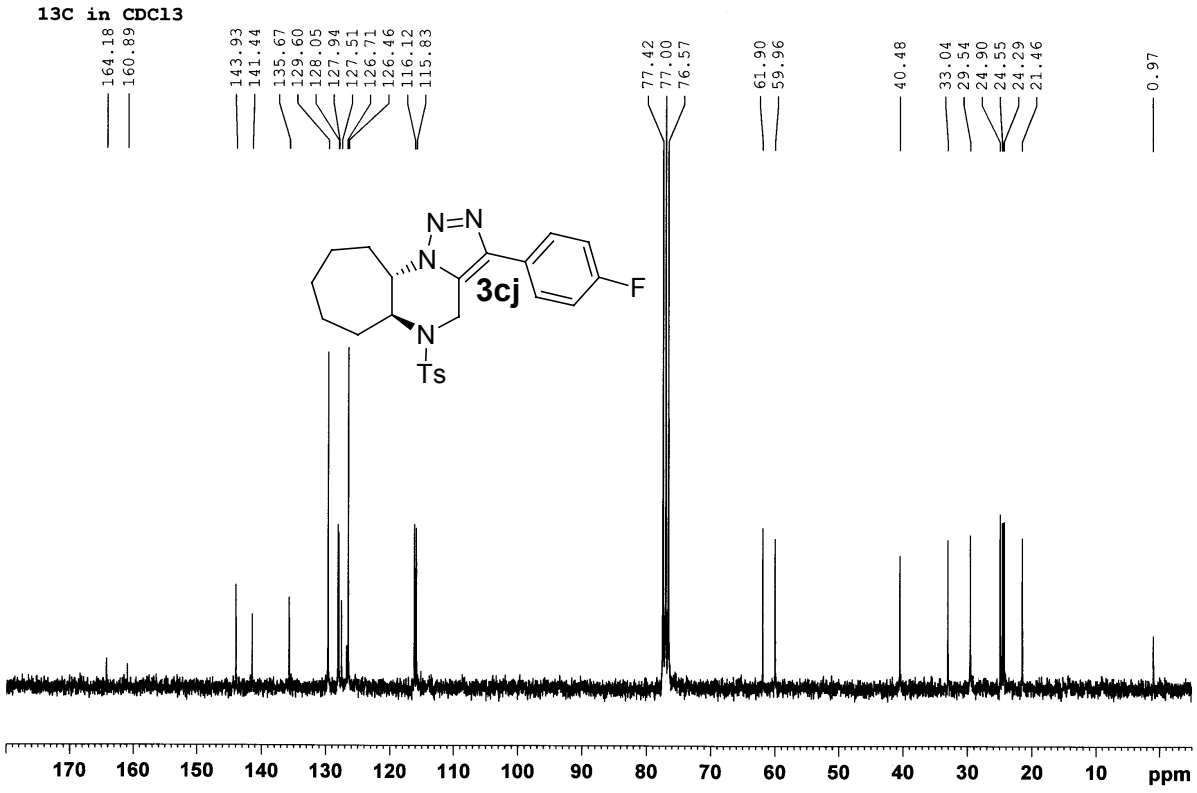
^{13}C NMR spectra of 3cg (600 MHz):



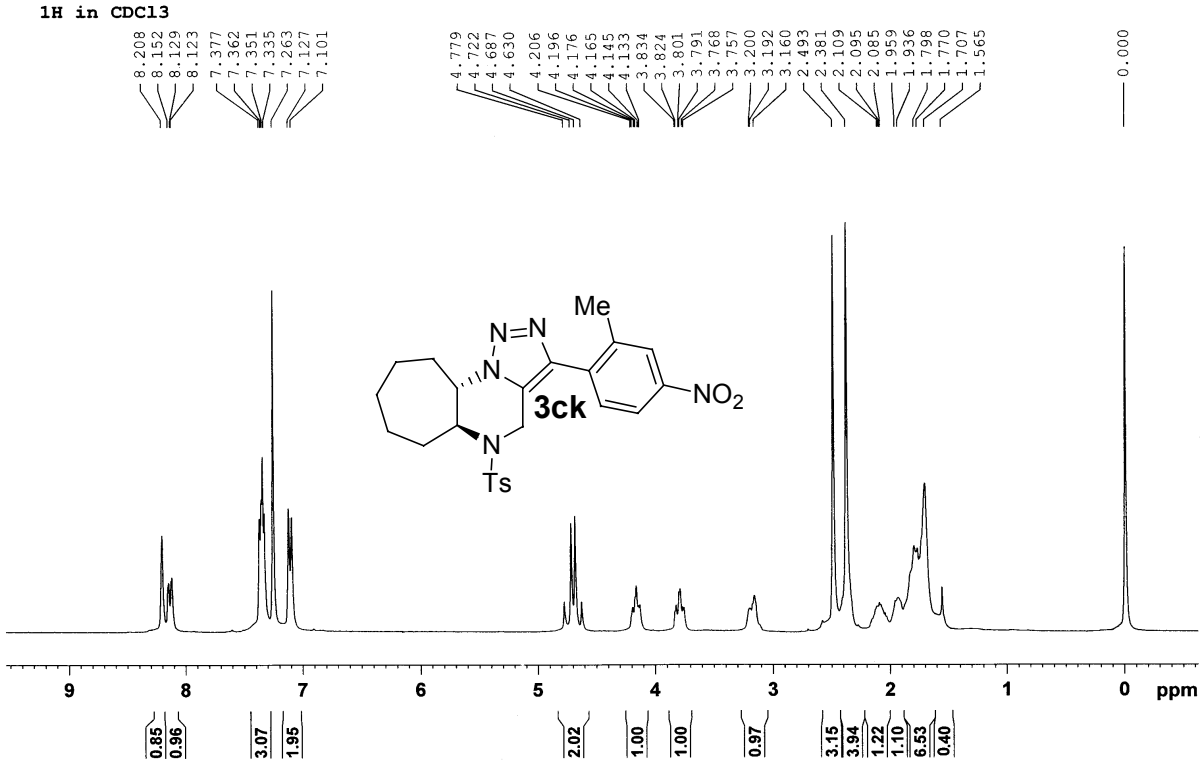
^{1}H NMR spectra of 3cj (600 MHz):



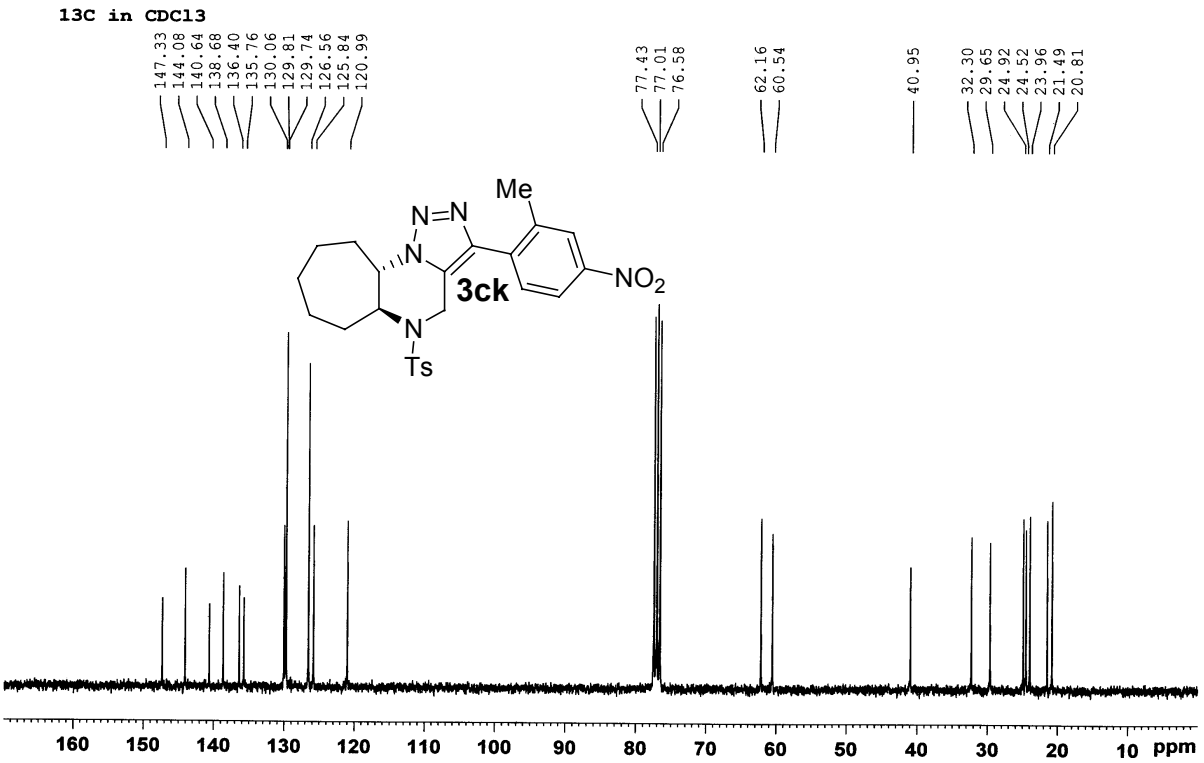
^{13}C NMR spectra of 3cj (300 MHz):



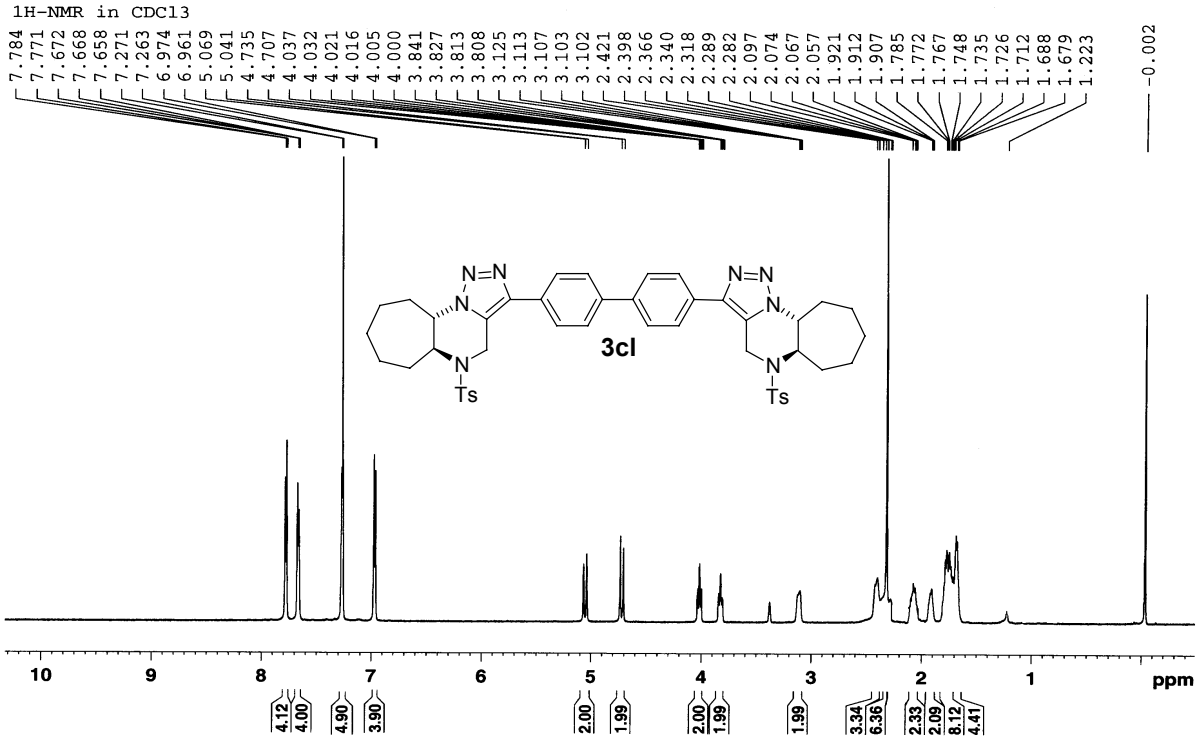
^{1}H NMR spectra of 3ck (300 MHz):



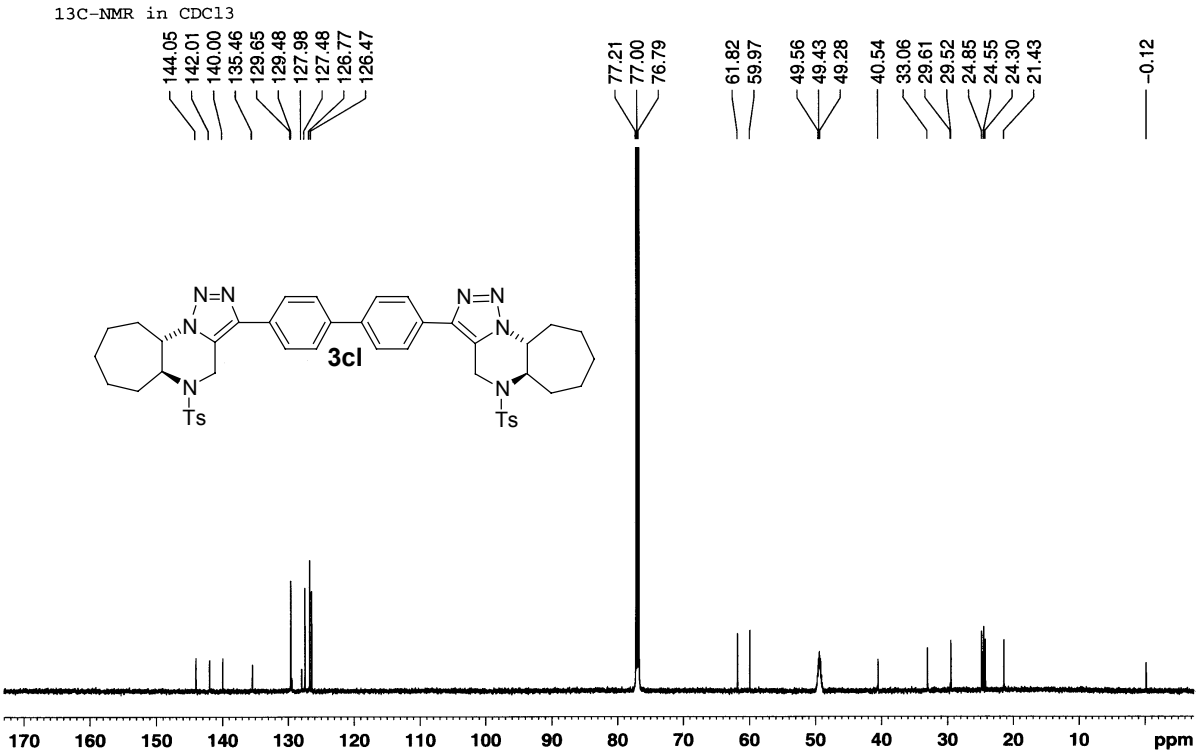
^{13}C NMR spectra of 3ck (300 MHz):



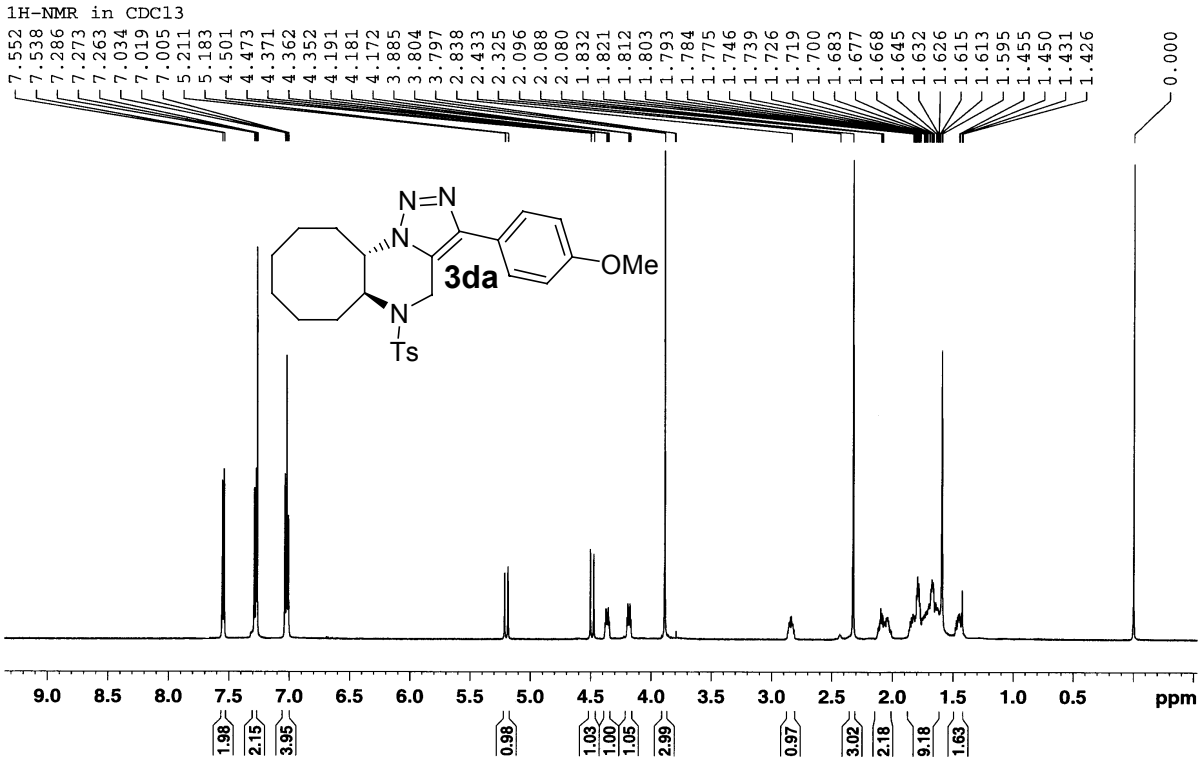
^{1}H NMR spectra of 3cl (600 MHz):



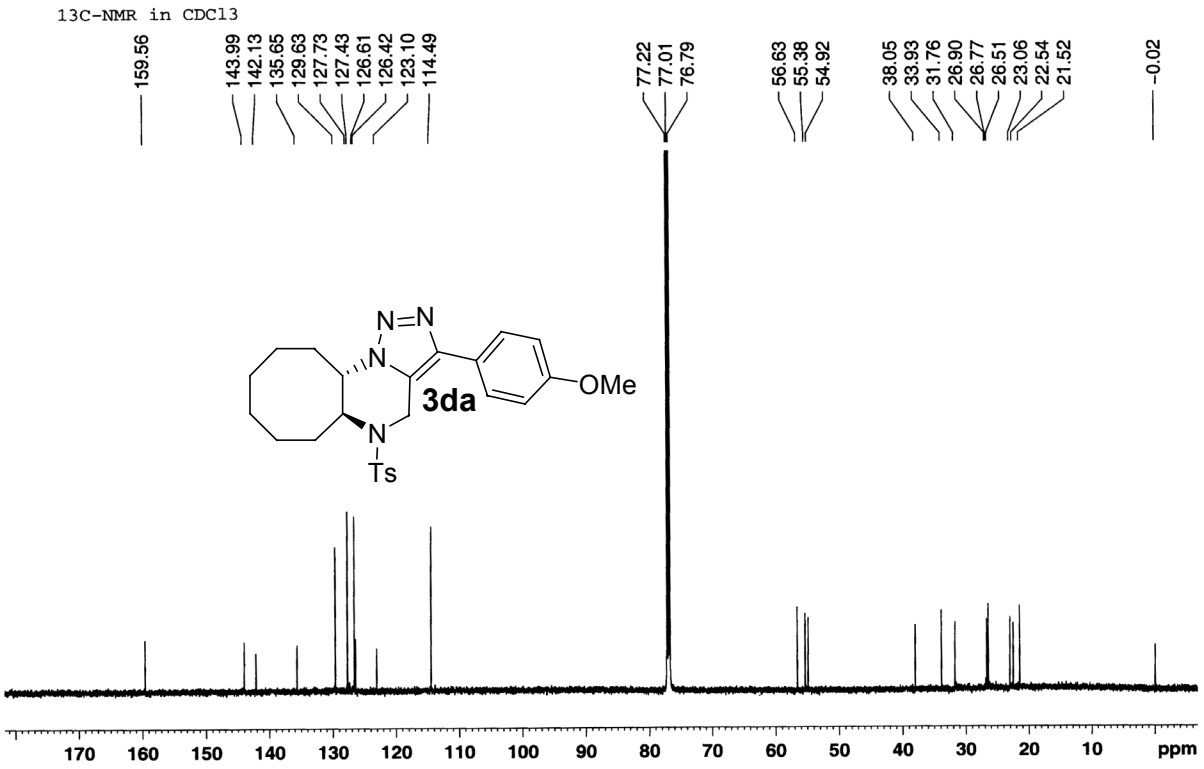
^{13}C NMR spectra of 3cl (600 MHz):



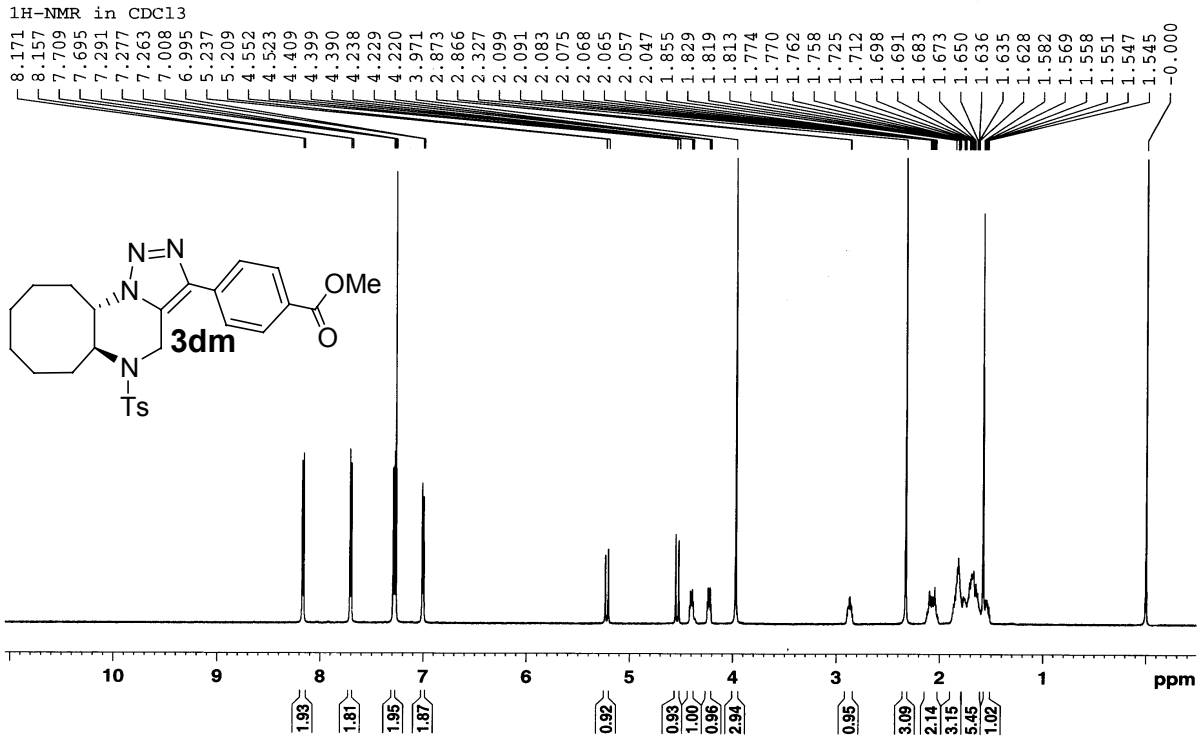
^{1}H NMR spectra of 3da (600 MHz):



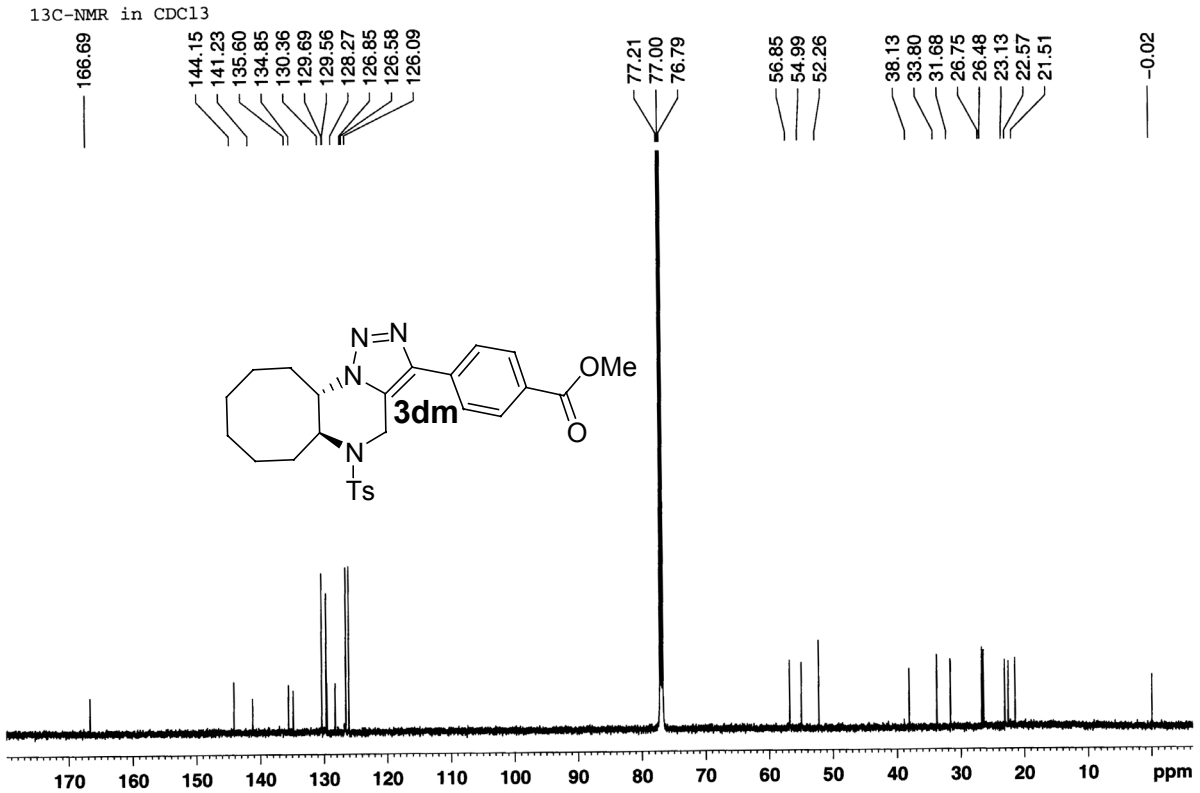
^{13}C NMR spectra of 3da (600 MHz):



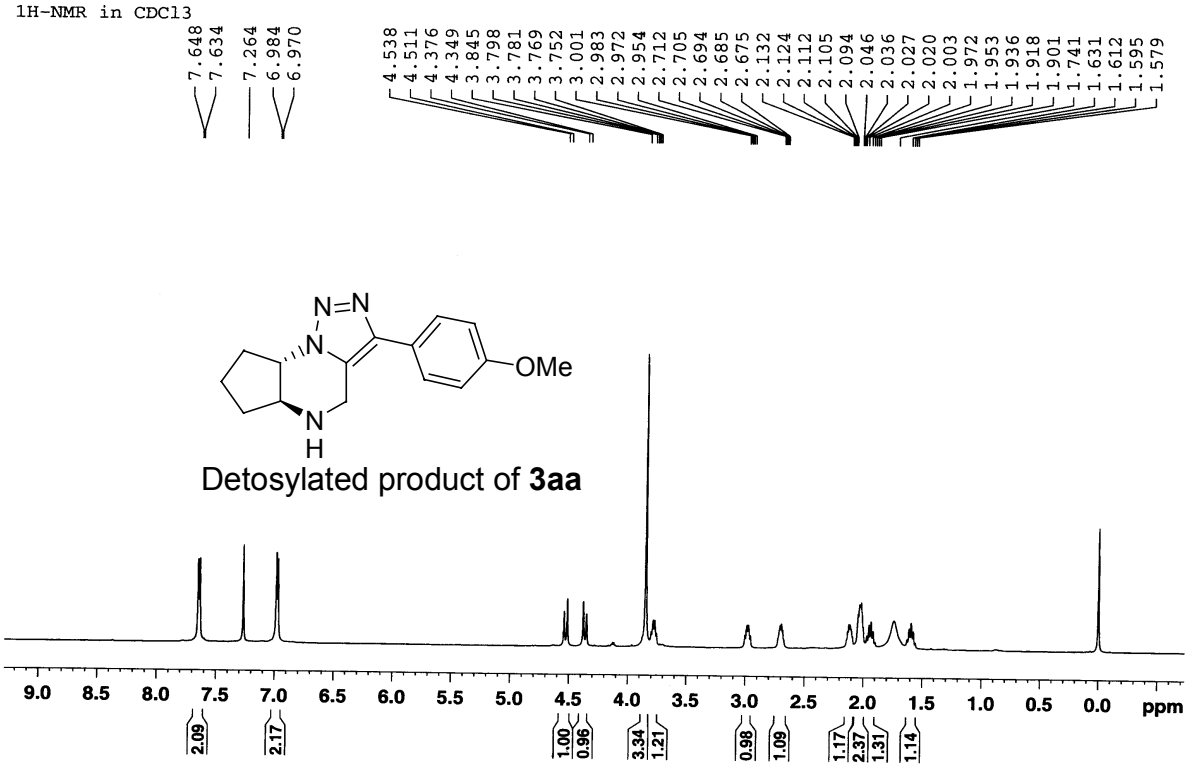
^{1}H NMR spectra of 3dm (600 MHz):



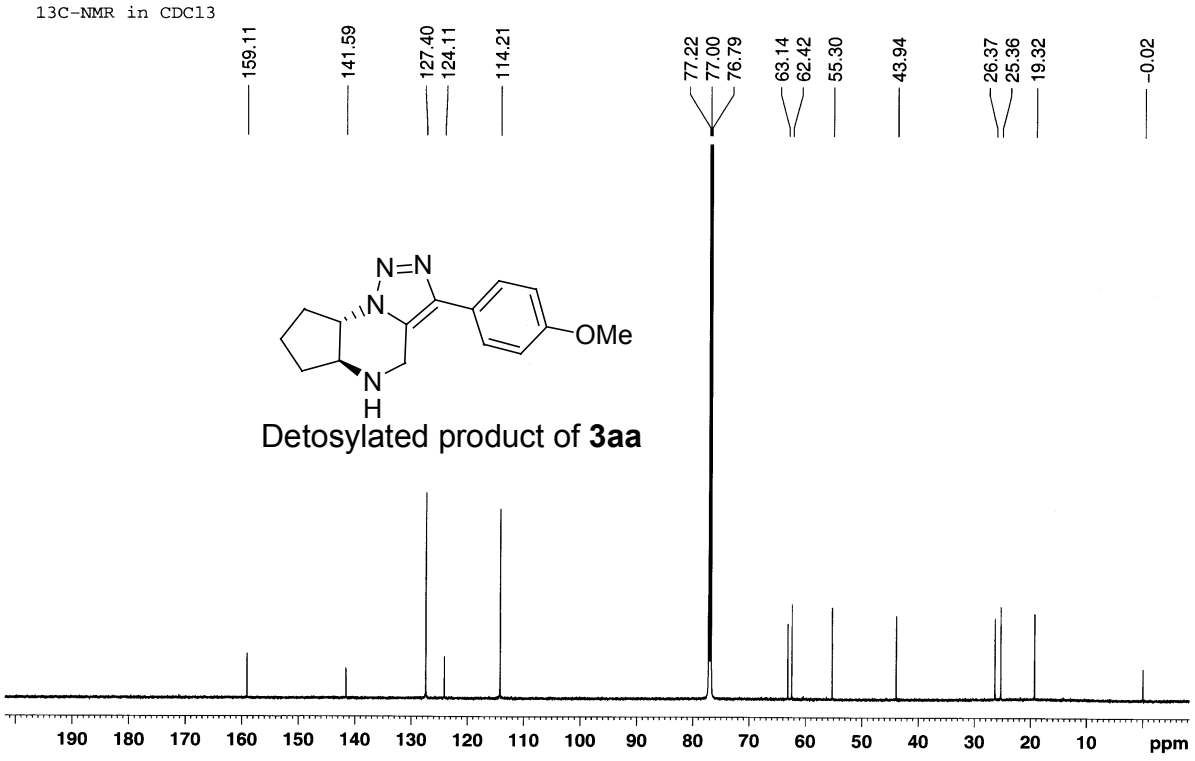
^{13}C NMR spectra of 3dm (600 MHz):



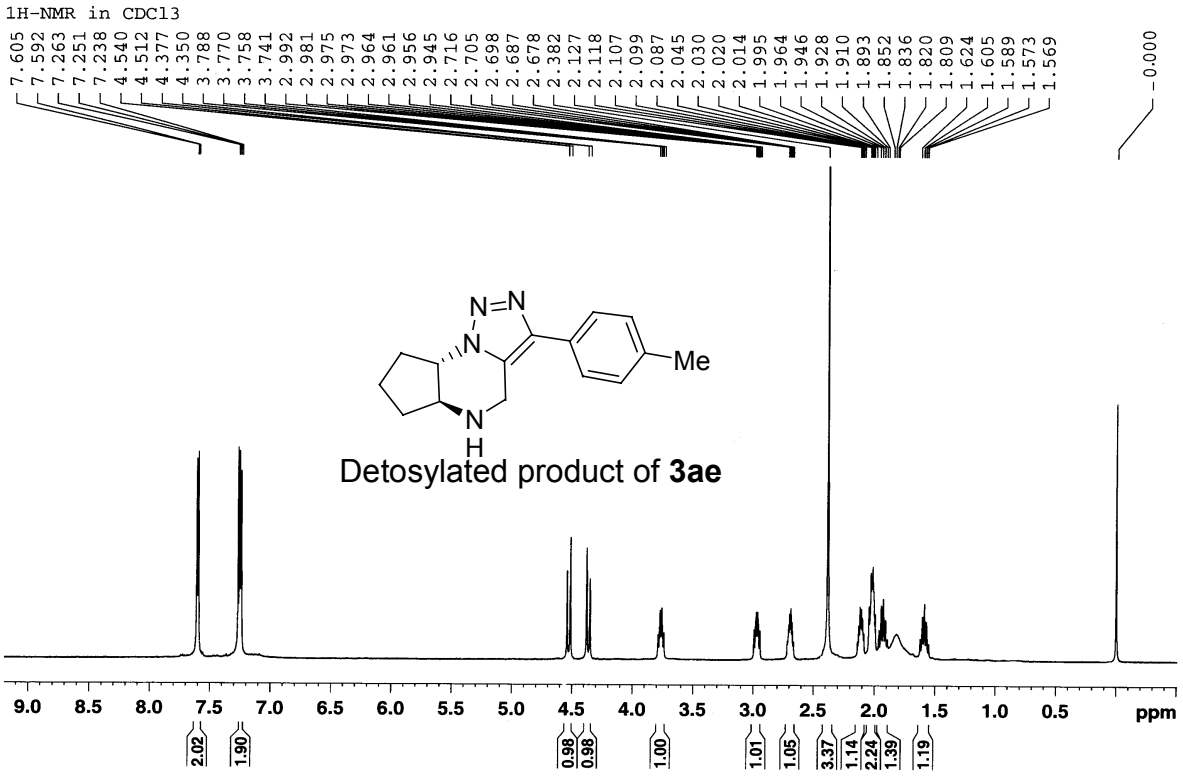
^{1}H NMR spectra of detosylated product of 3aa (600 MHz):



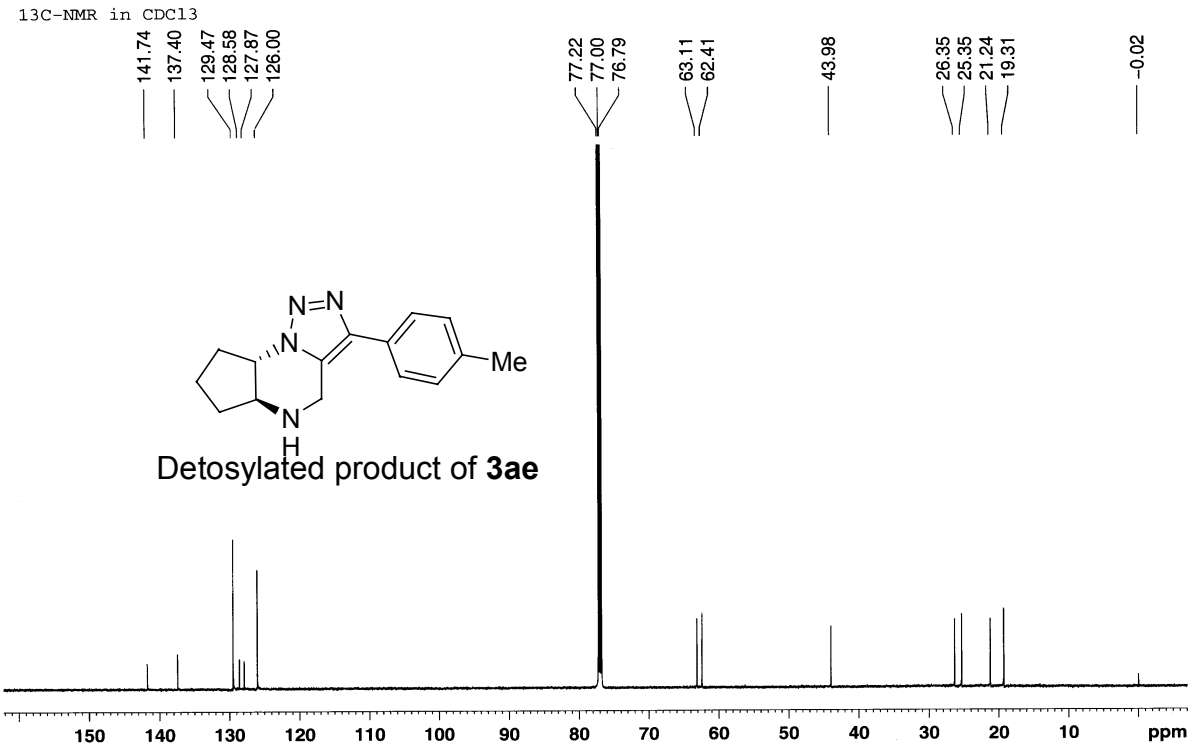
^{13}C NMR spectra of detosylated product of 3aa (600 MHz):



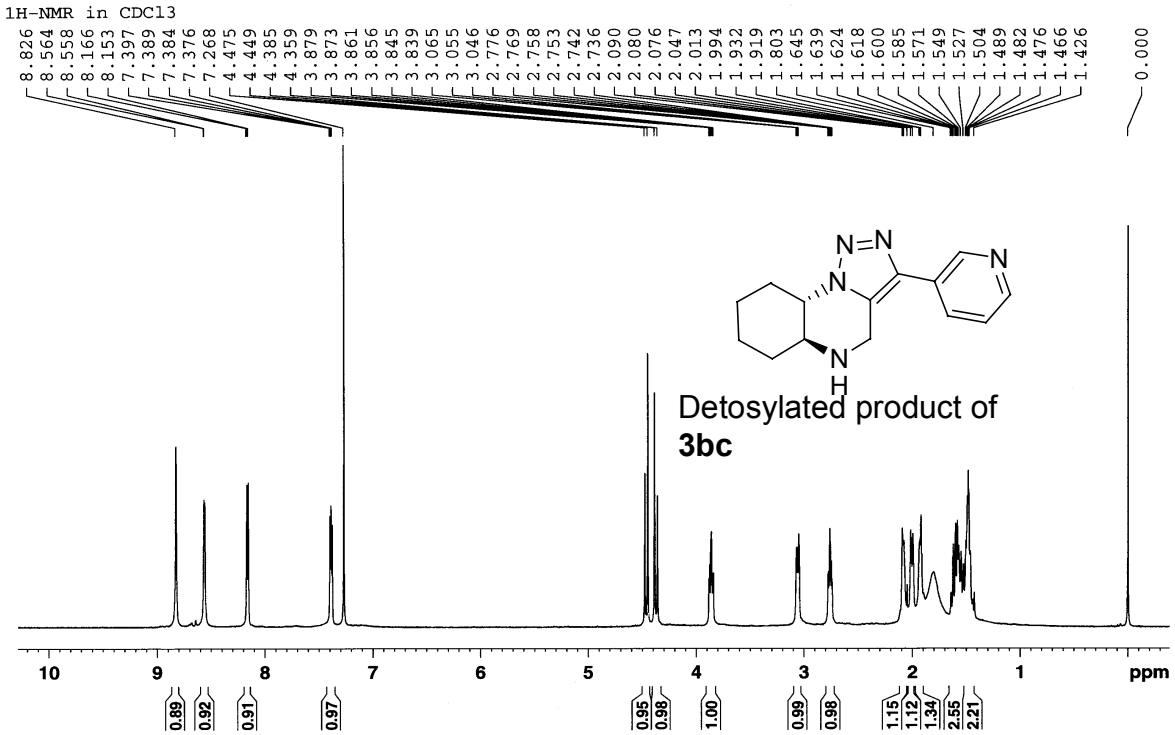
^{1}H NMR spectra of detosylated product of 3ae (600 MHz):



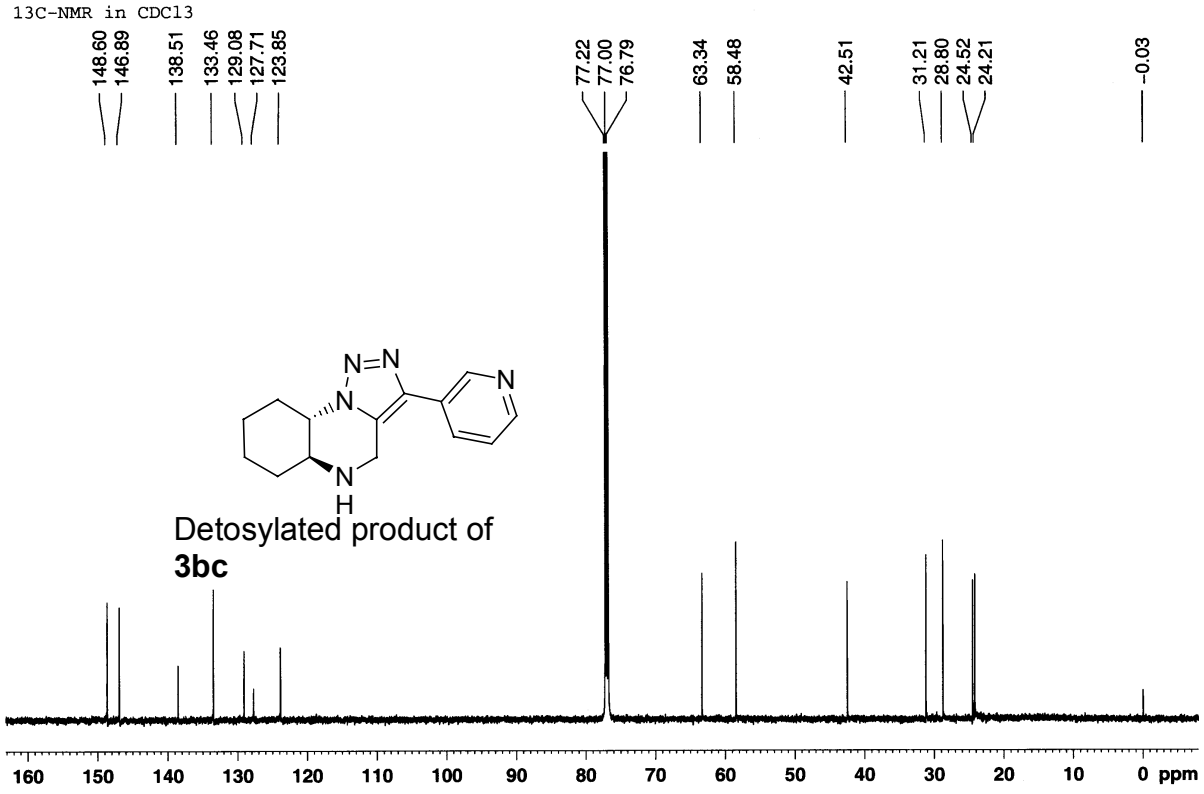
^{13}C NMR spectra of detosylated product of 3ae (600 MHz):



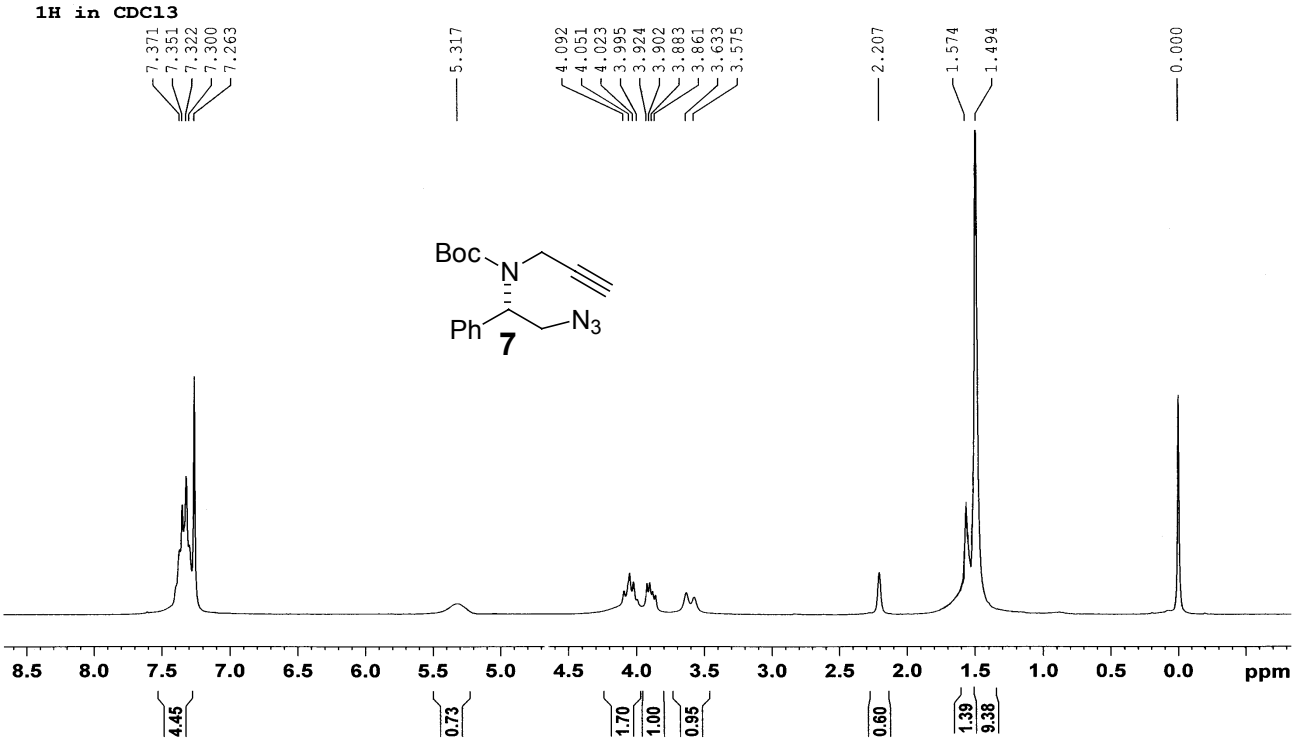
^{1}H NMR spectra of detosylated product of 3bc (600 MHz):



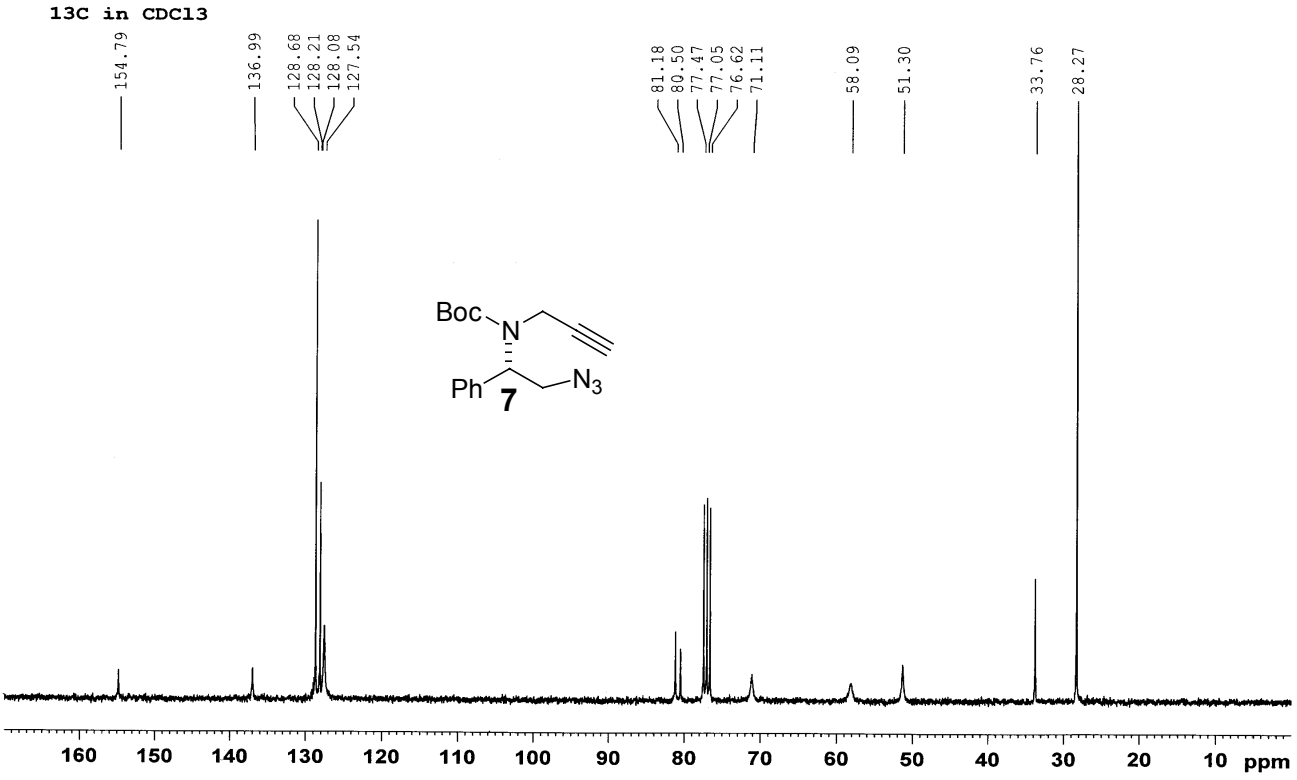
^{13}C NMR spectra of detosylated product of 3bc (600 MHz):



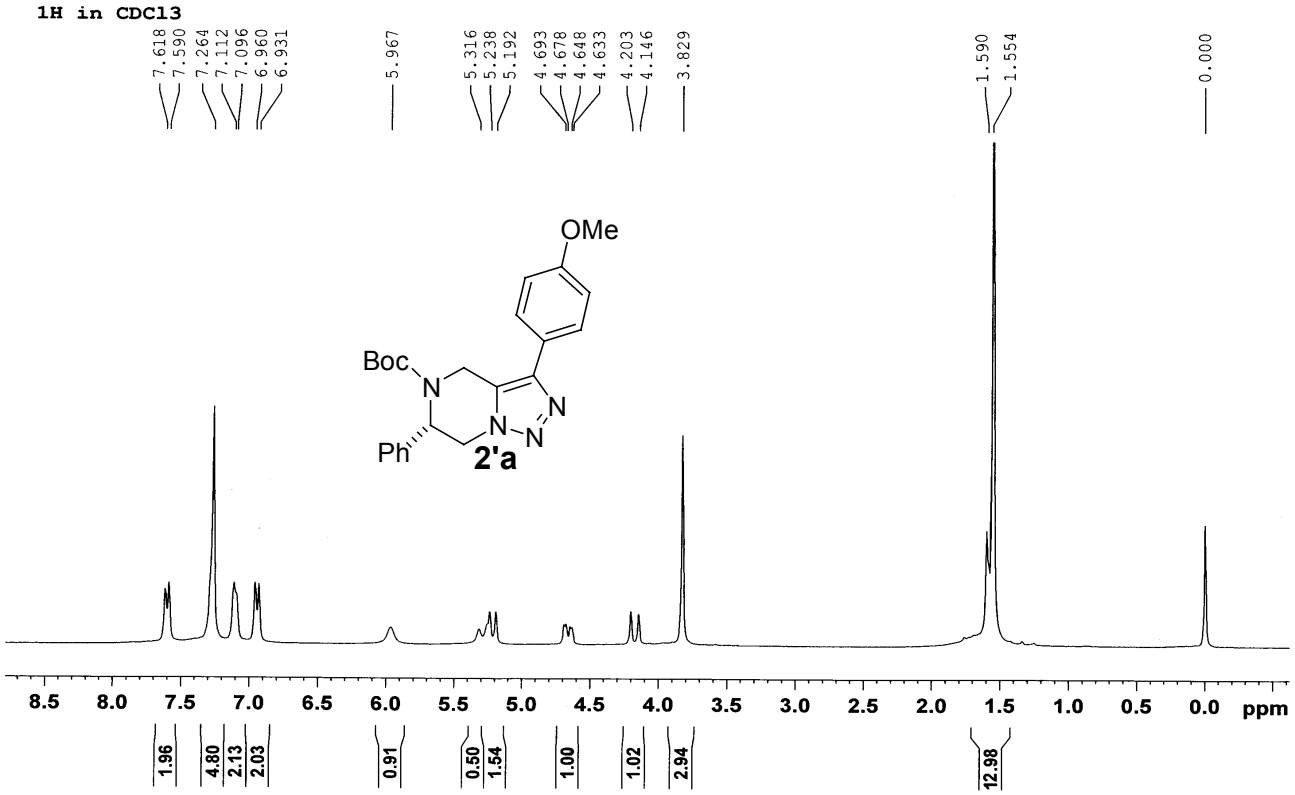
^{1}H NMR spectra of 7 (600 MHz):



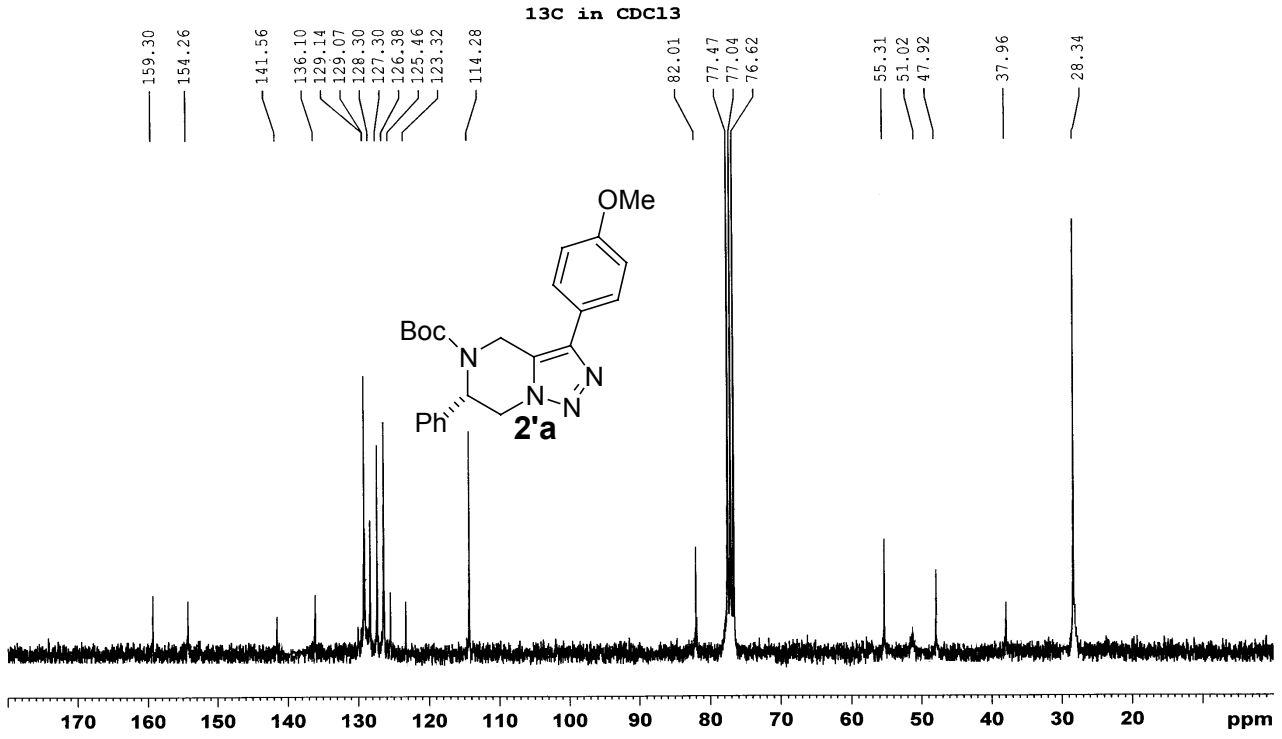
^{13}C NMR spectra of 7 (75 MHz):



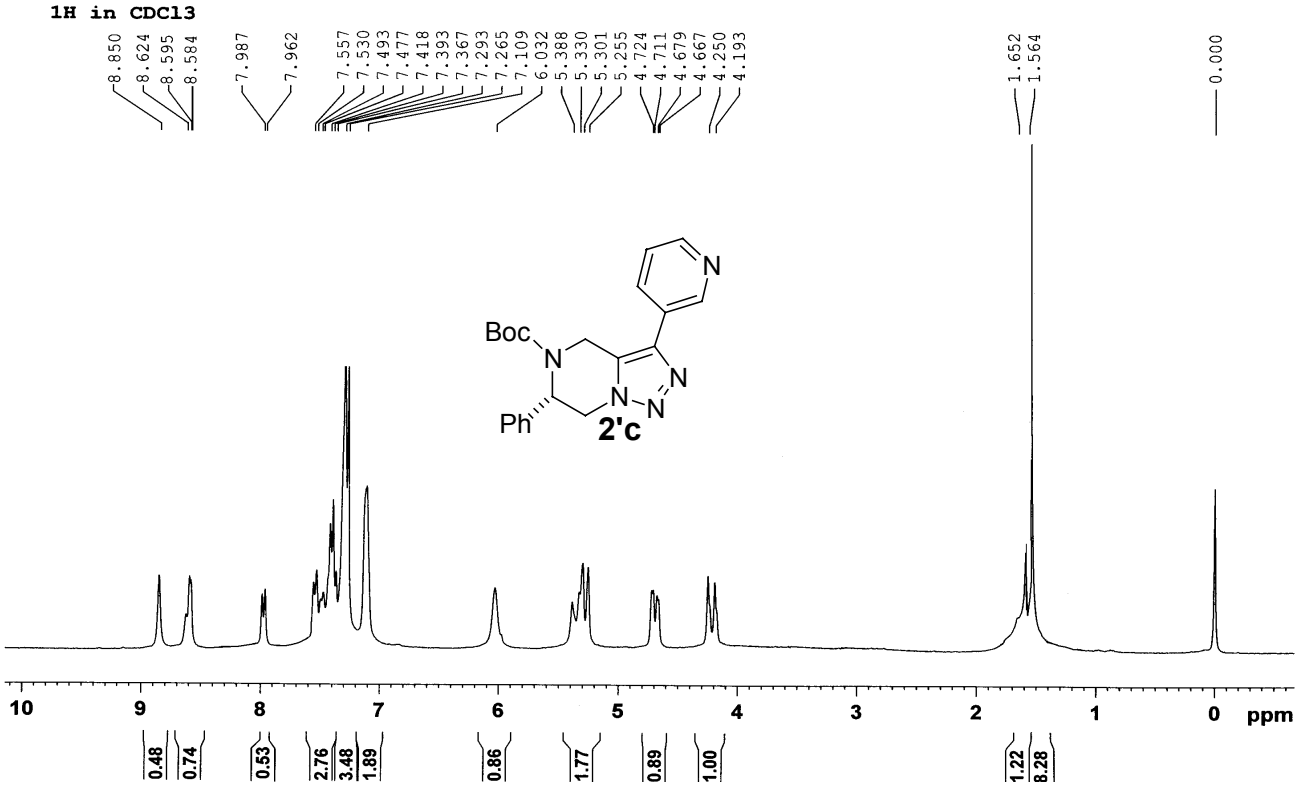
^{1}H NMR spectra of 2′a (300 MHz):



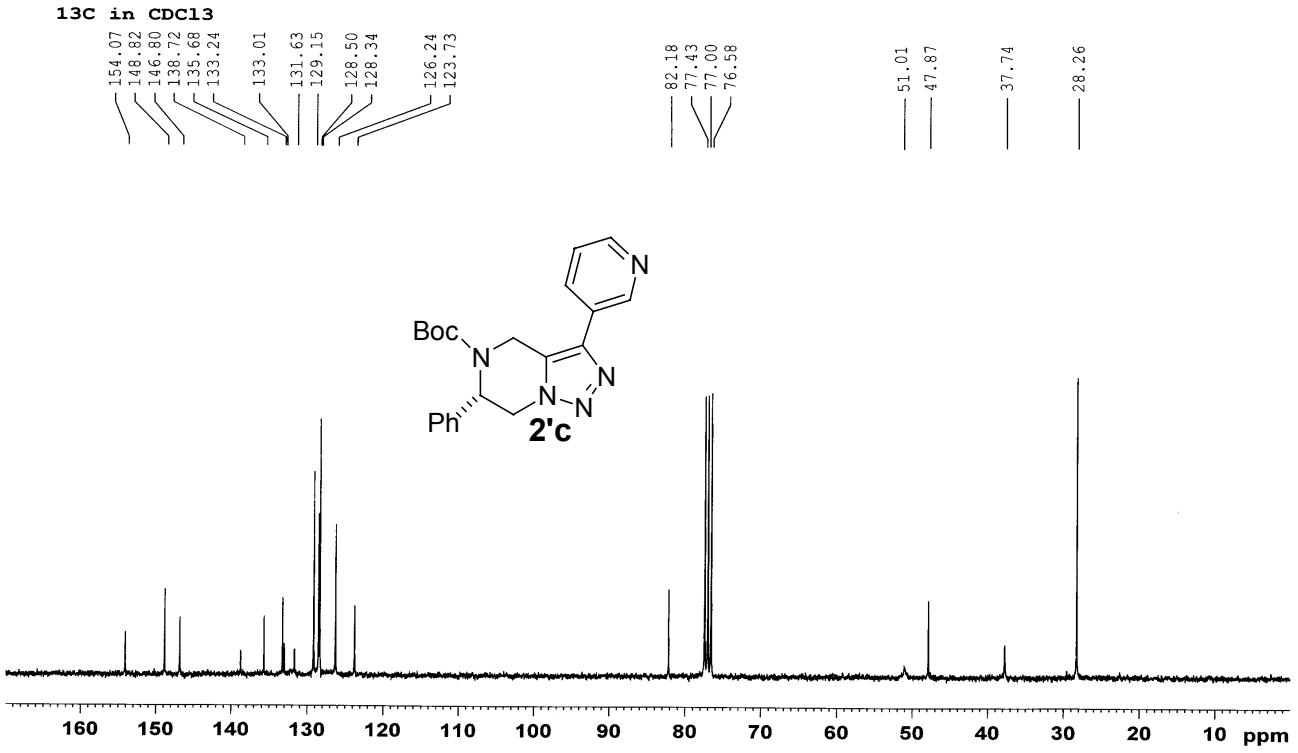
^{13}C NMR spectra of 2′a (75 MHz):



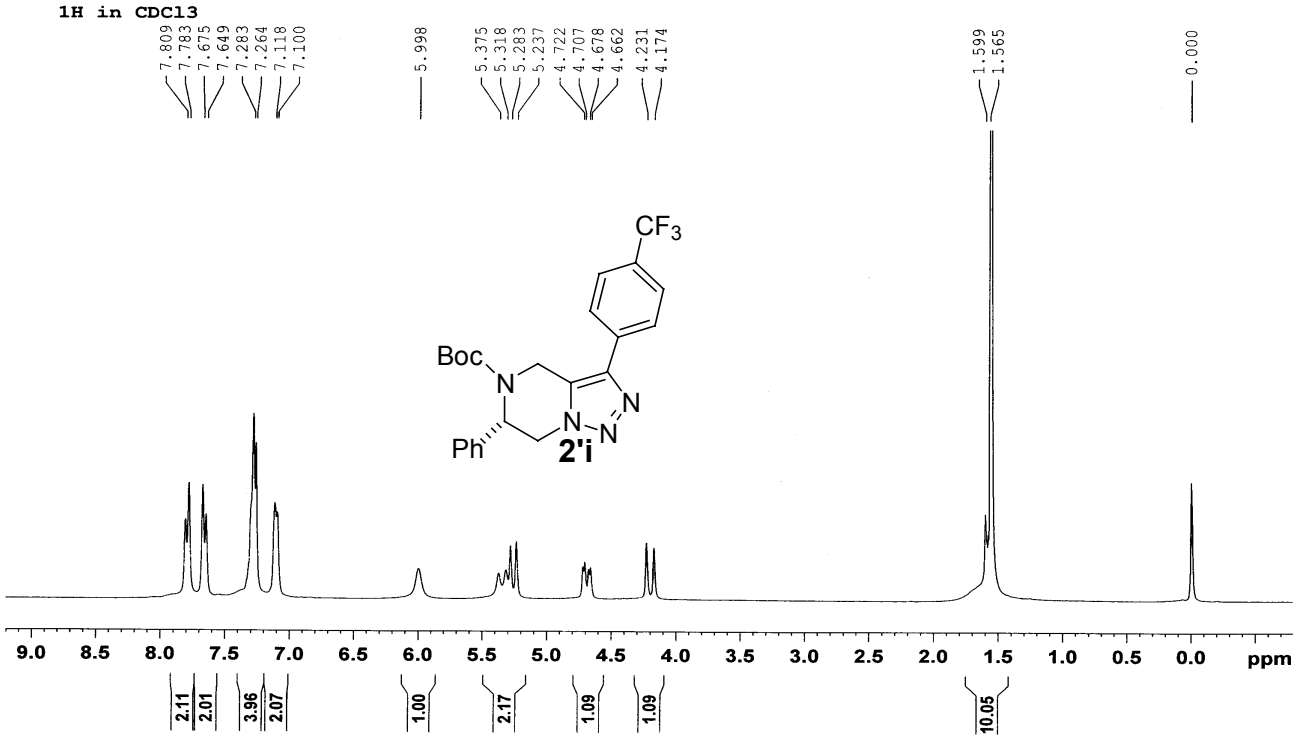
^{1}H NMR spectra of 2′c (300 MHz):



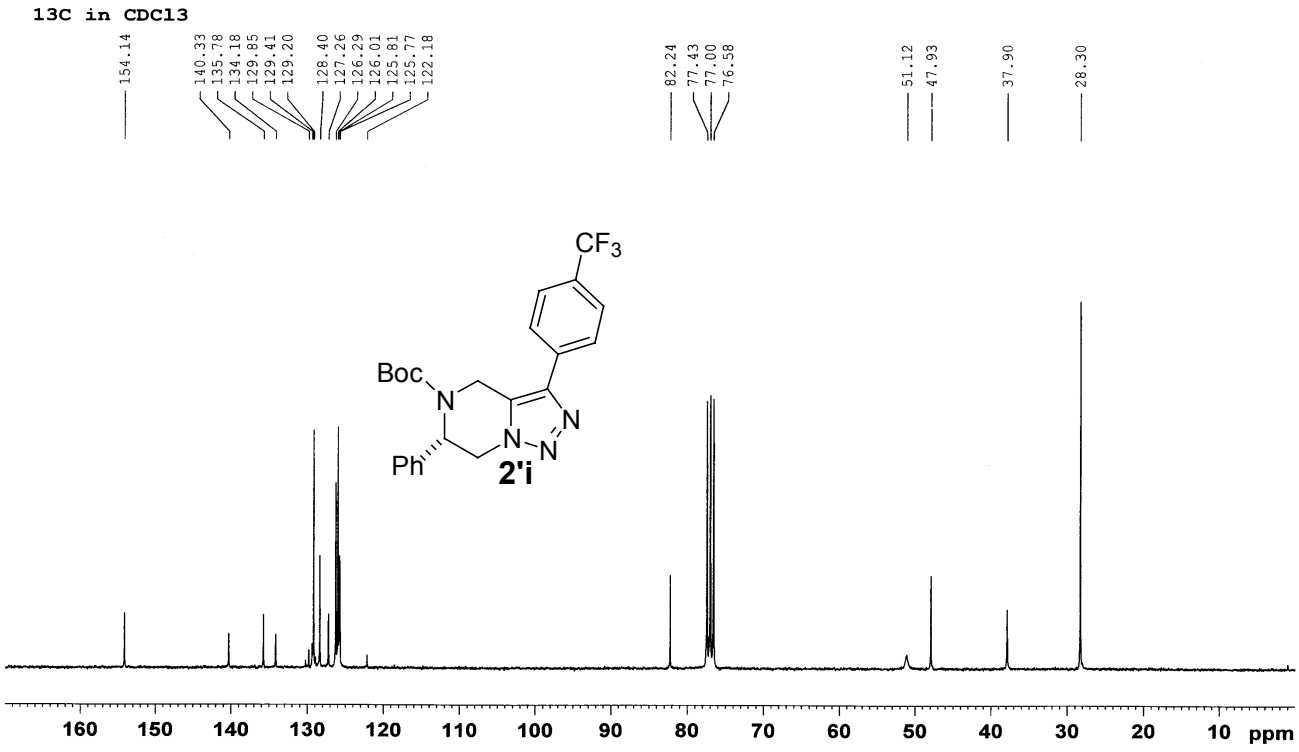
^{13}C NMR spectra of 2′c (75 MHz):



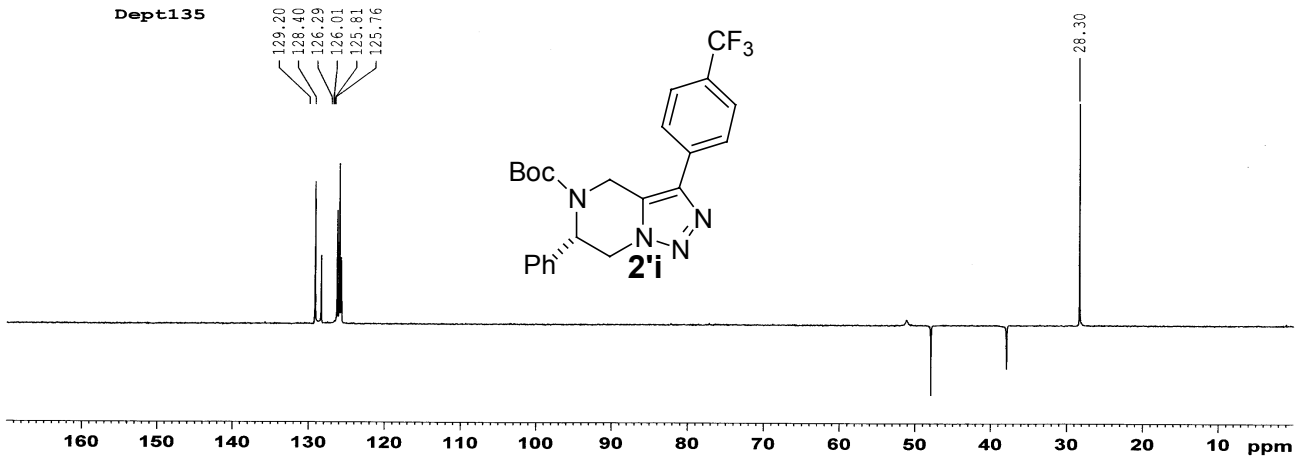
^{1}H NMR spectra of 2′i (300 MHz):



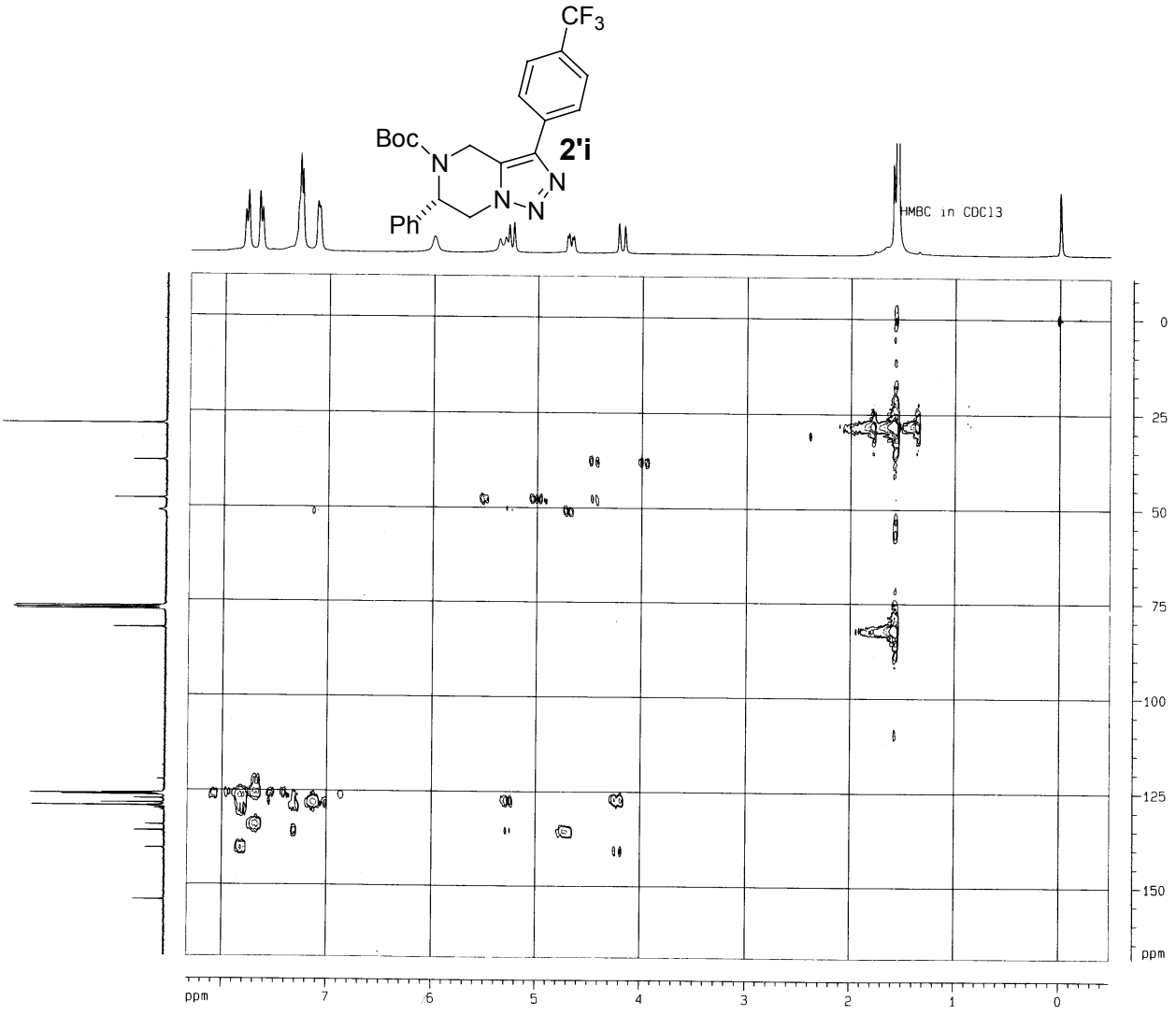
^{13}C NMR spectra of 2′i (75 MHz):



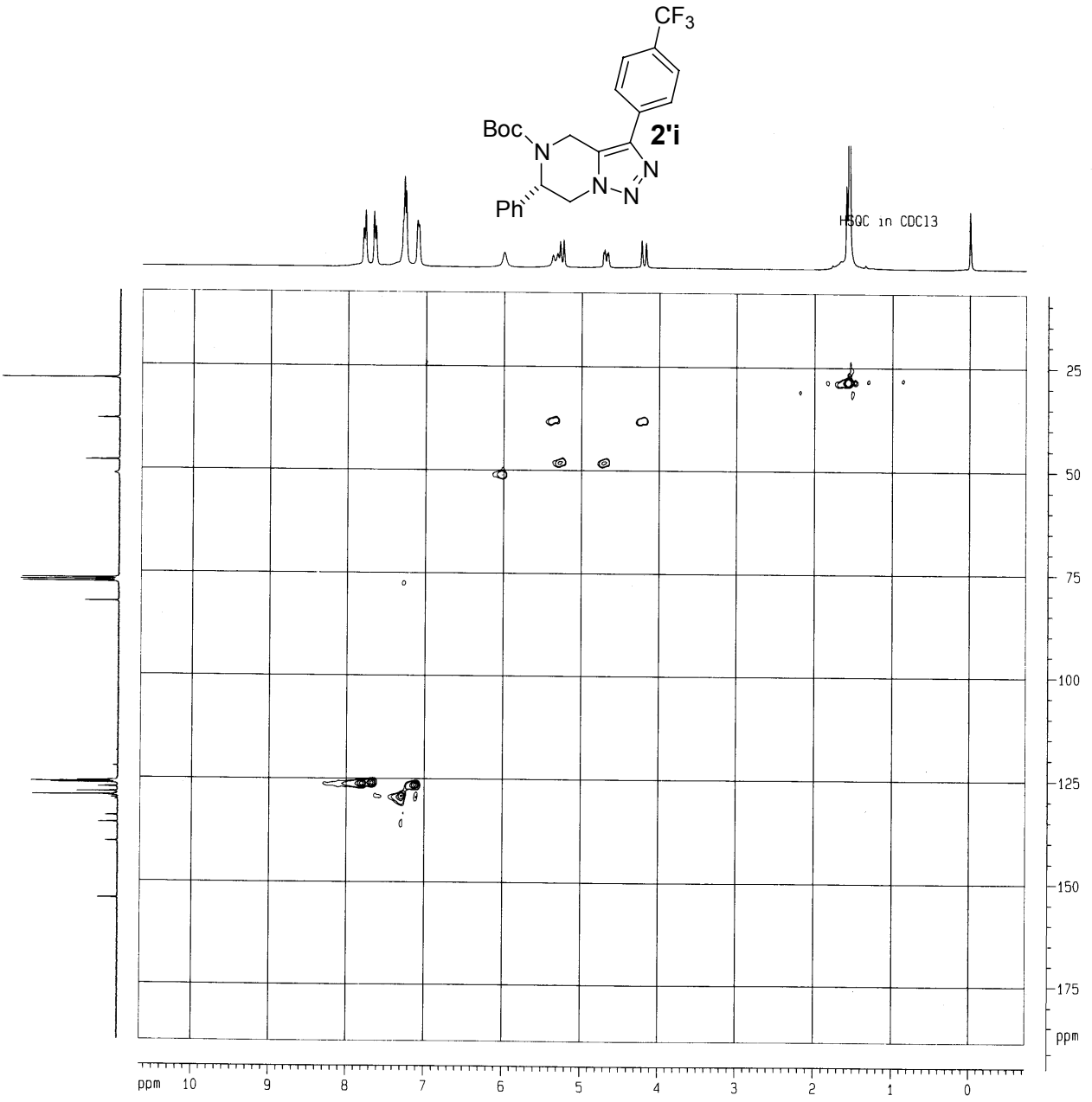
DEPT of 2′i (75 MHz):



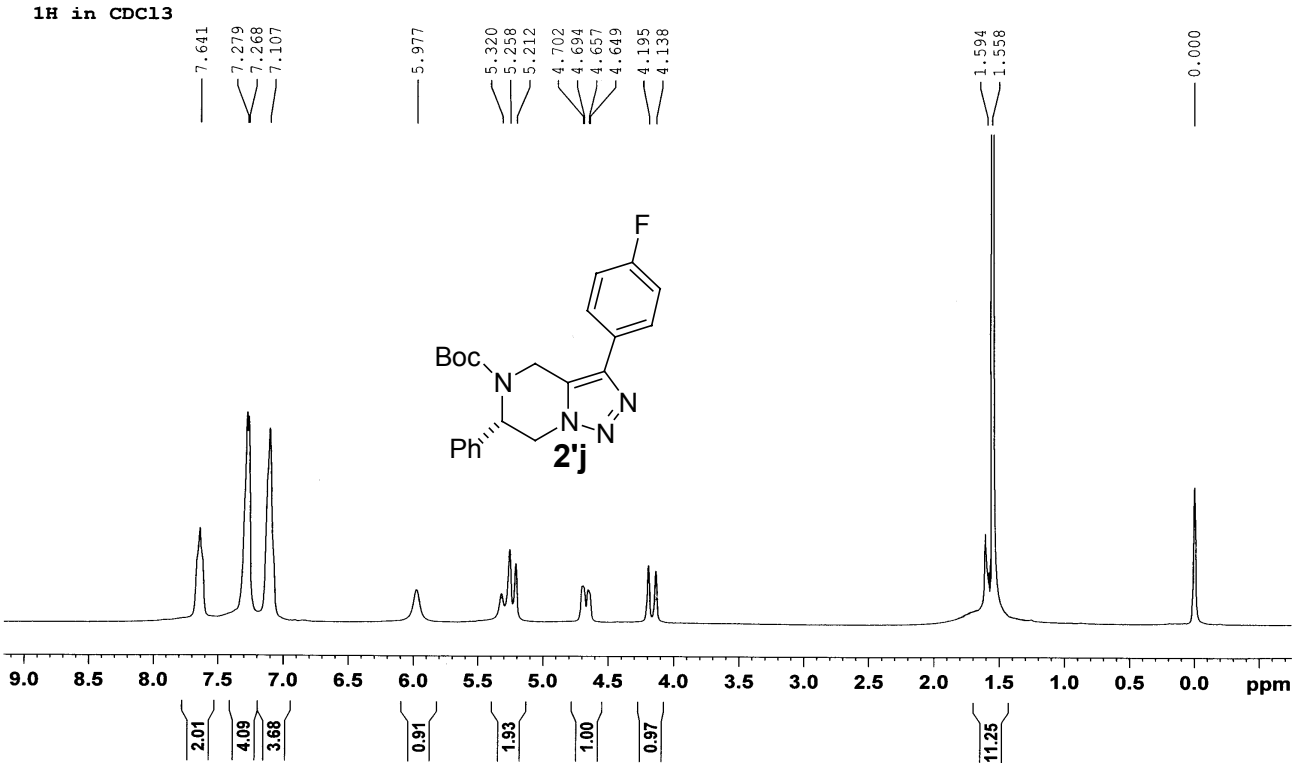
HMBC of 3′i:



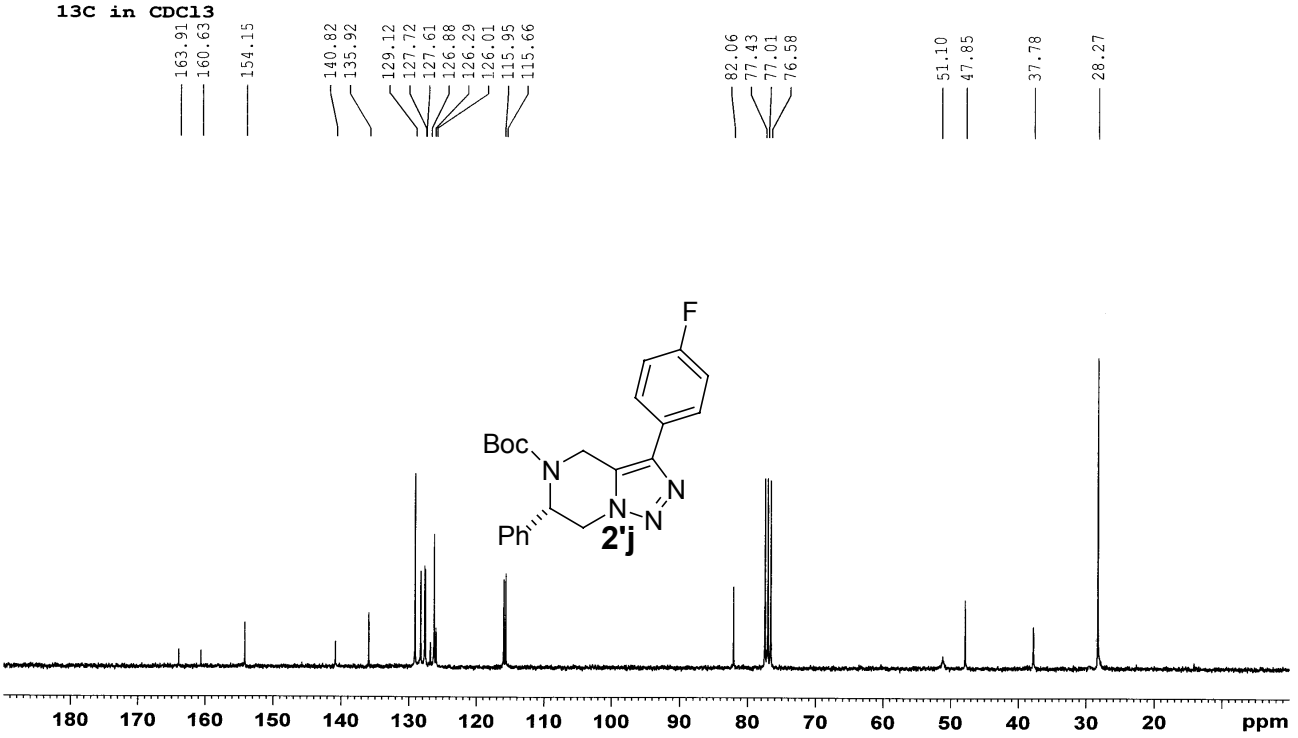
HSQC of 2′i:


CF3
Boc
N
2'i
N
N
N
Ph
HSQC in CDCl3
25
50
75
100
125
150
175
ppm
ppm 10 9 8 7 6 5 4 3 2 1 0

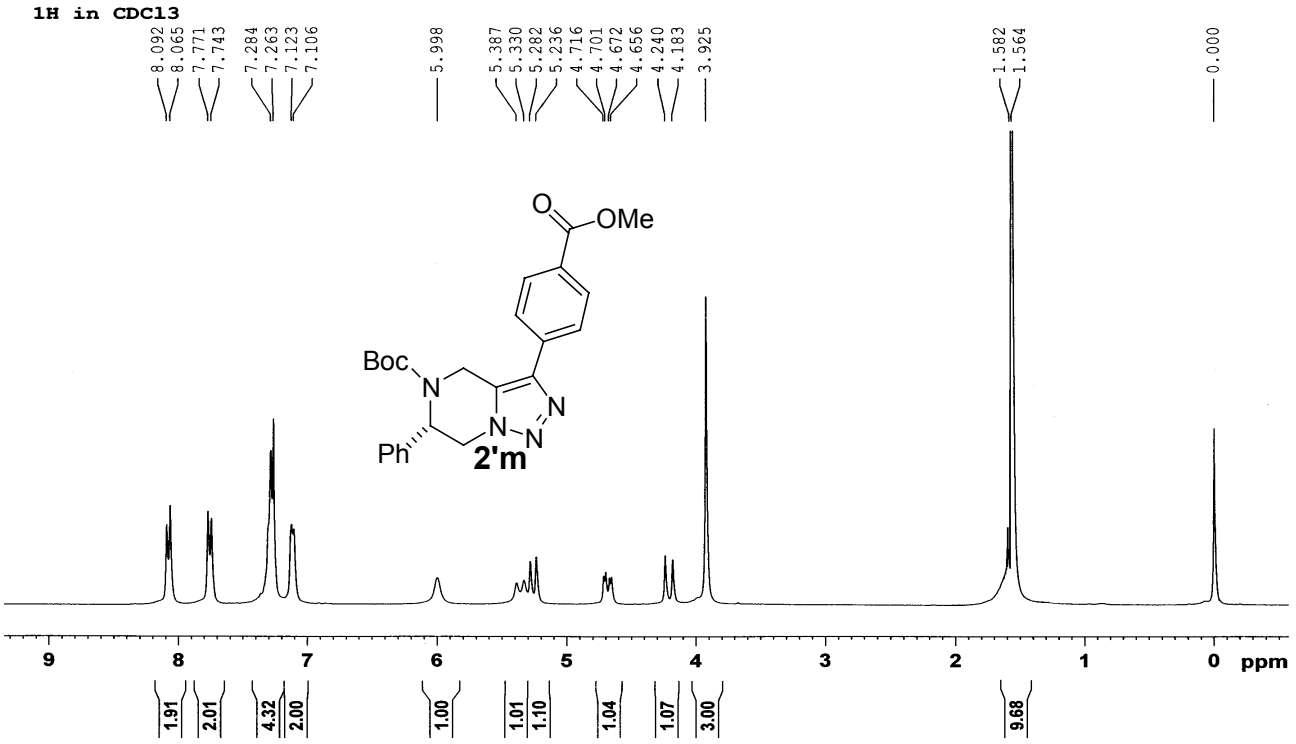
^{1}H NMR spectra of 2′j (300 MHz):



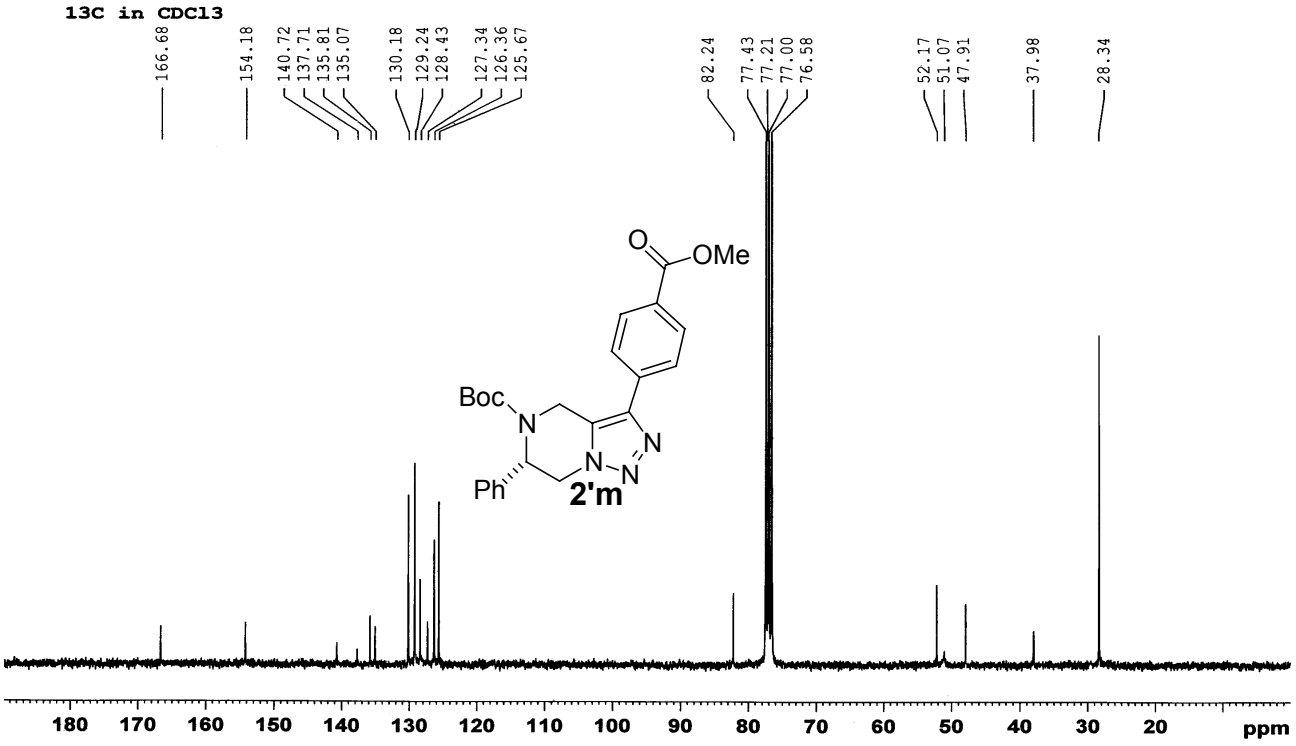
^{13}C NMR spectra of 2′j (75 MHz):



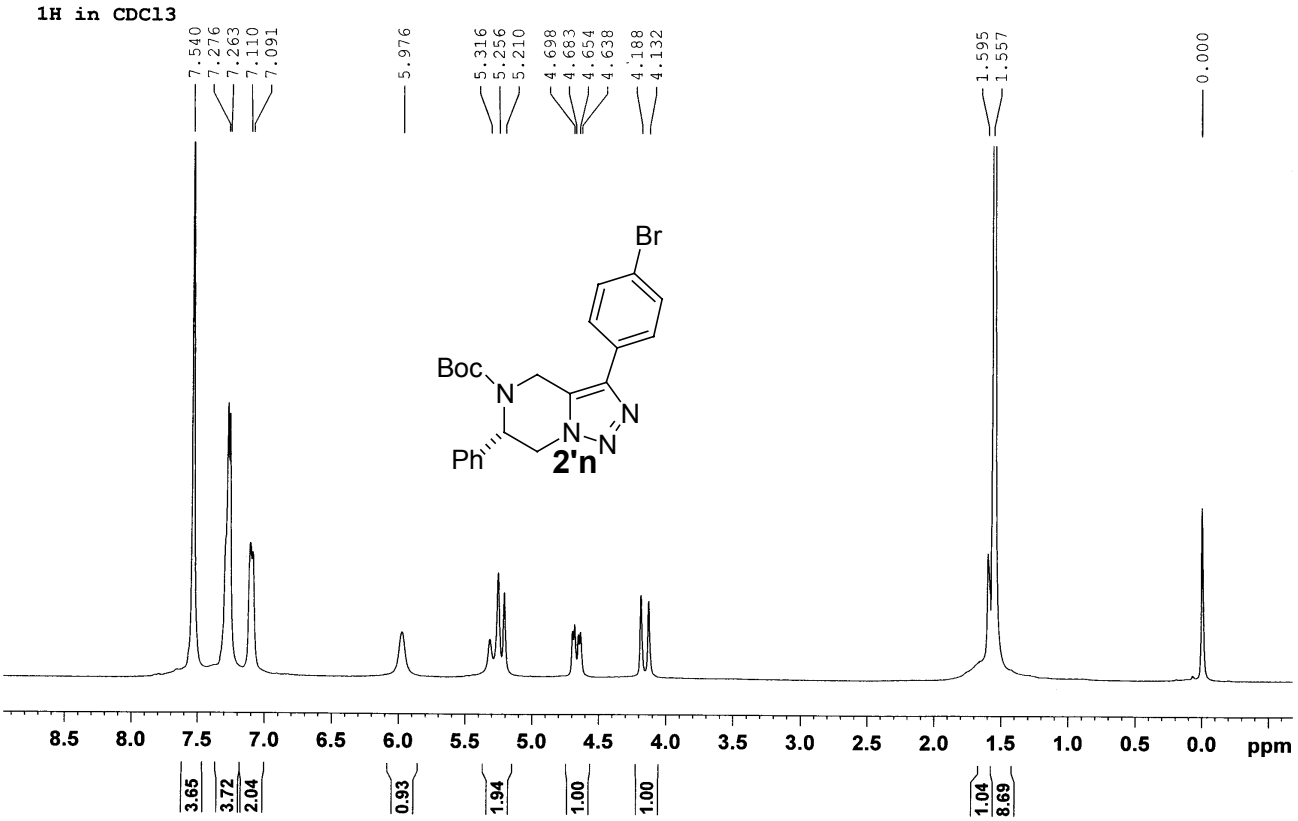
^{1}H NMR spectra of 2′m (300 MHz):



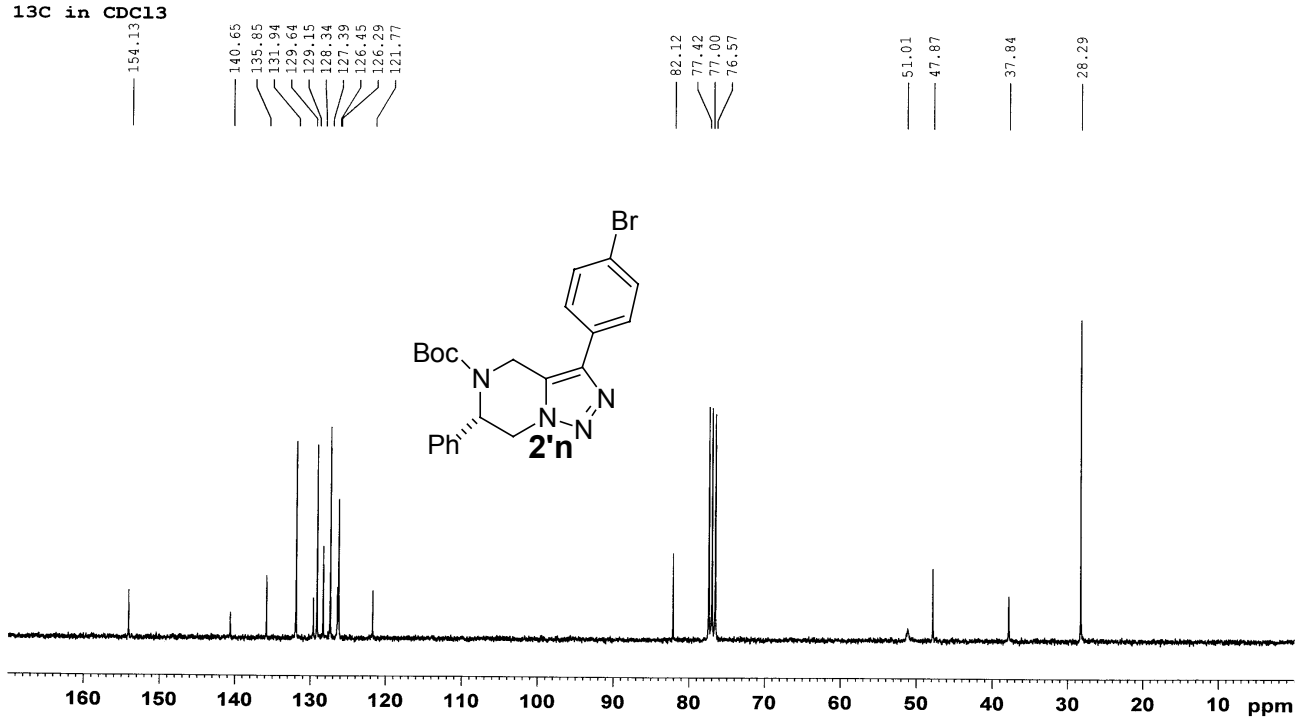
^{13}C NMR spectra of 2′m (75 MHz):



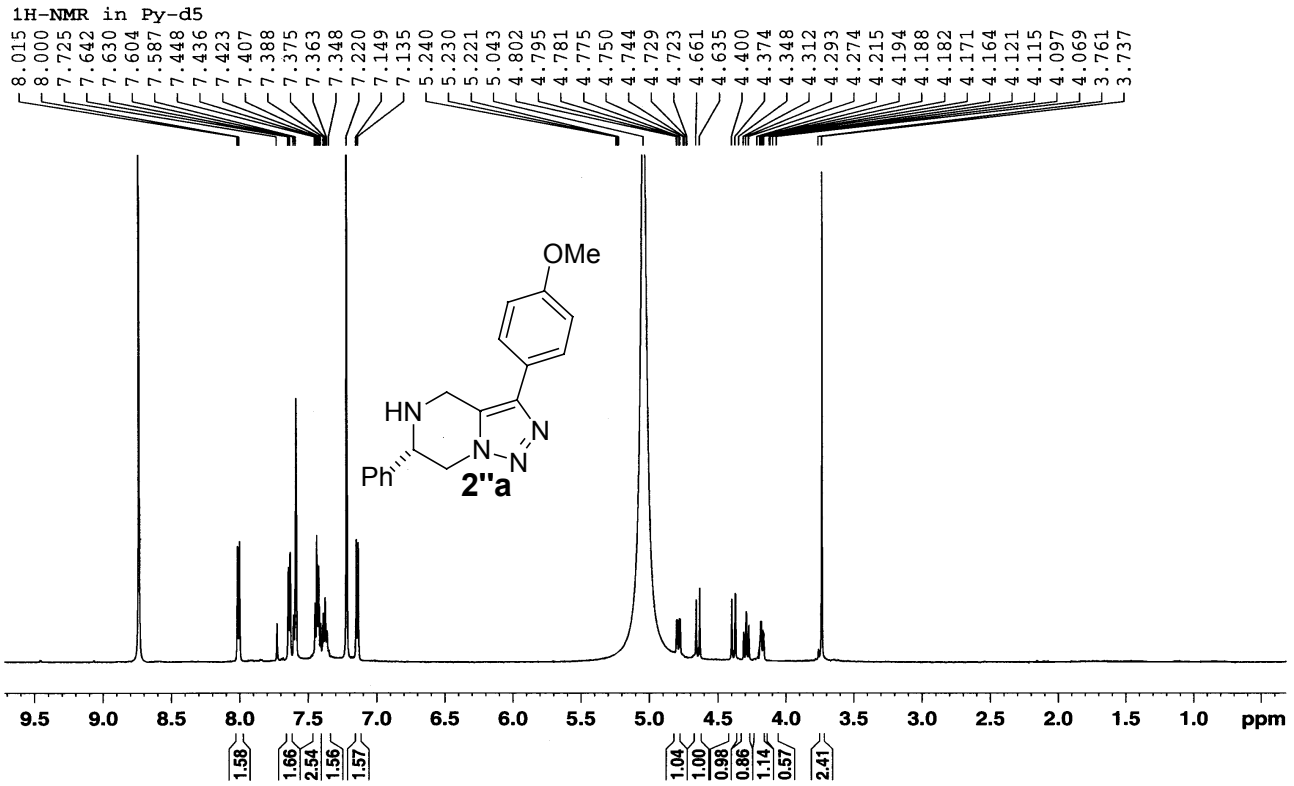
^{1}H NMR spectra of 2′n (300 MHz):



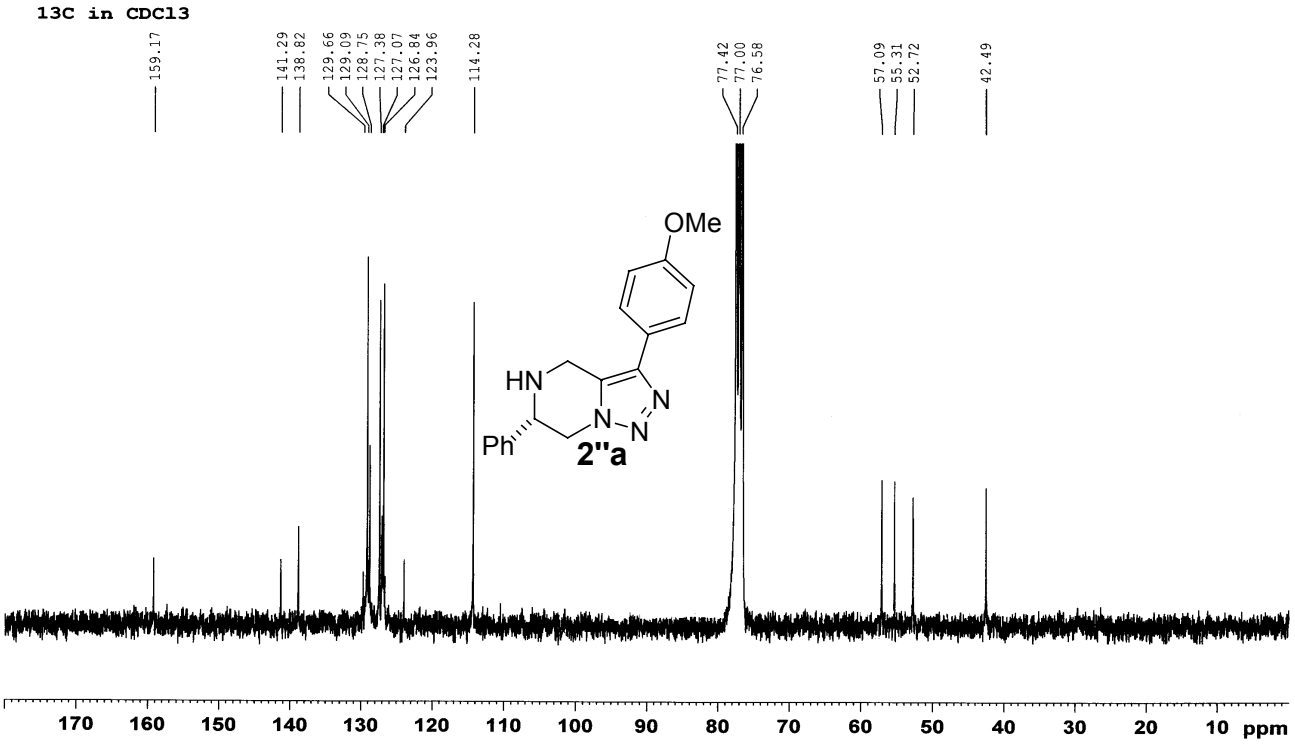
^{13}C NMR spectra of 2′n (75 MHz):



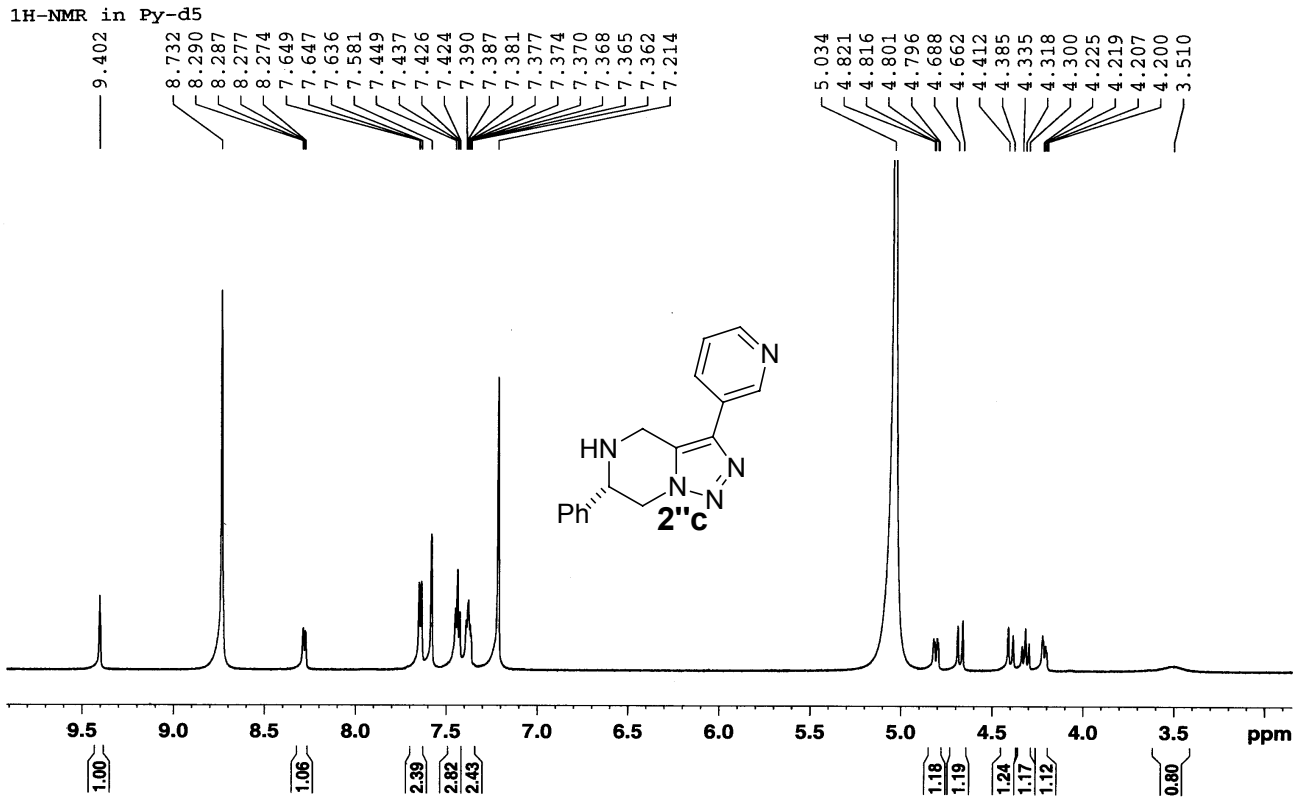
^{1}H NMR spectra of 2′′a (600 MHz):



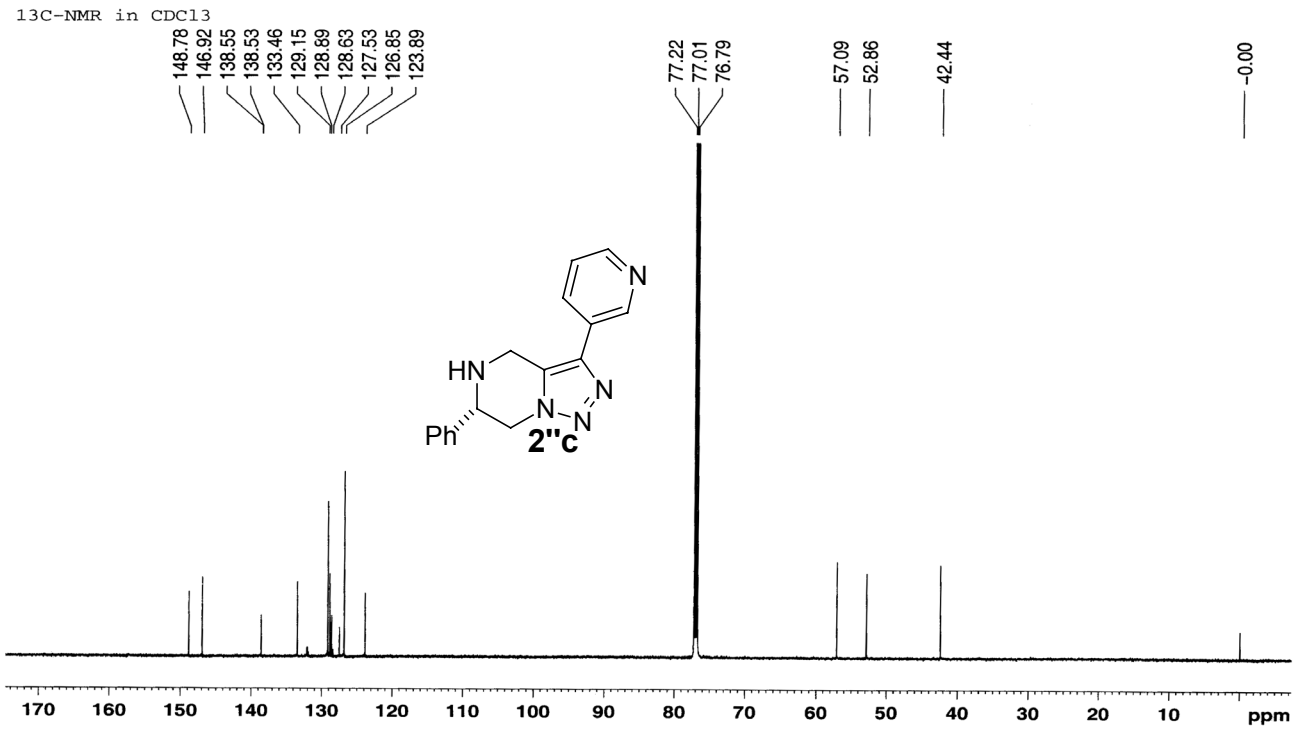
^{13}C NMR spectra of 2′′a (75 MHz):



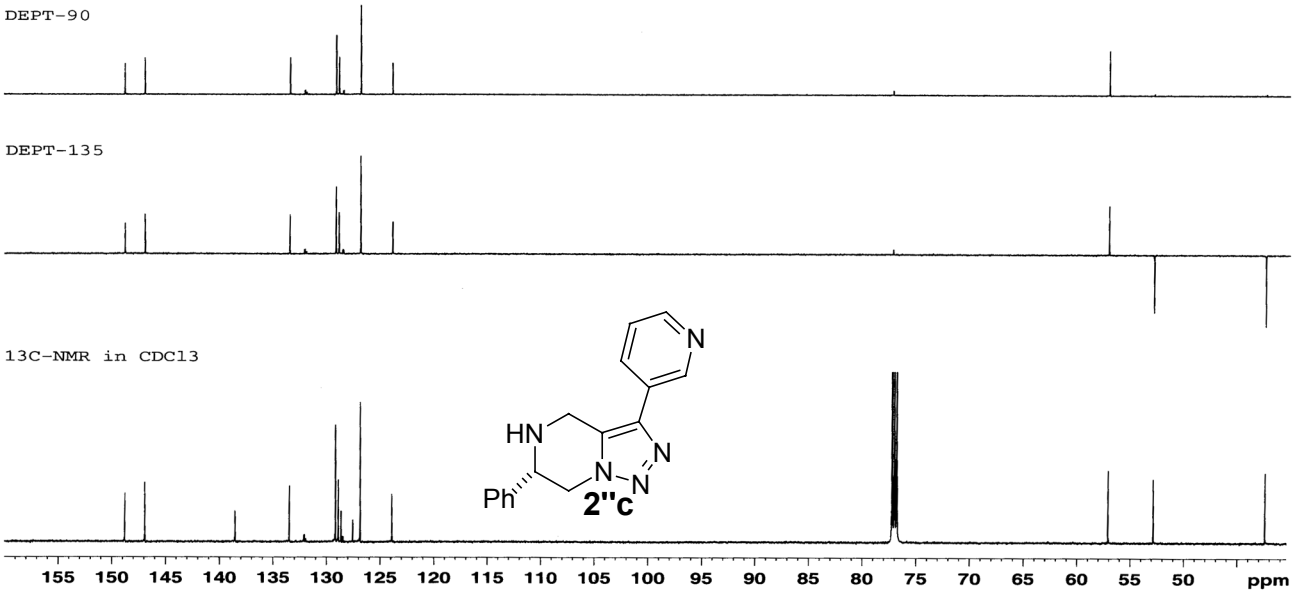
^{1}H NMR spectra of 2″c (600 MHz):



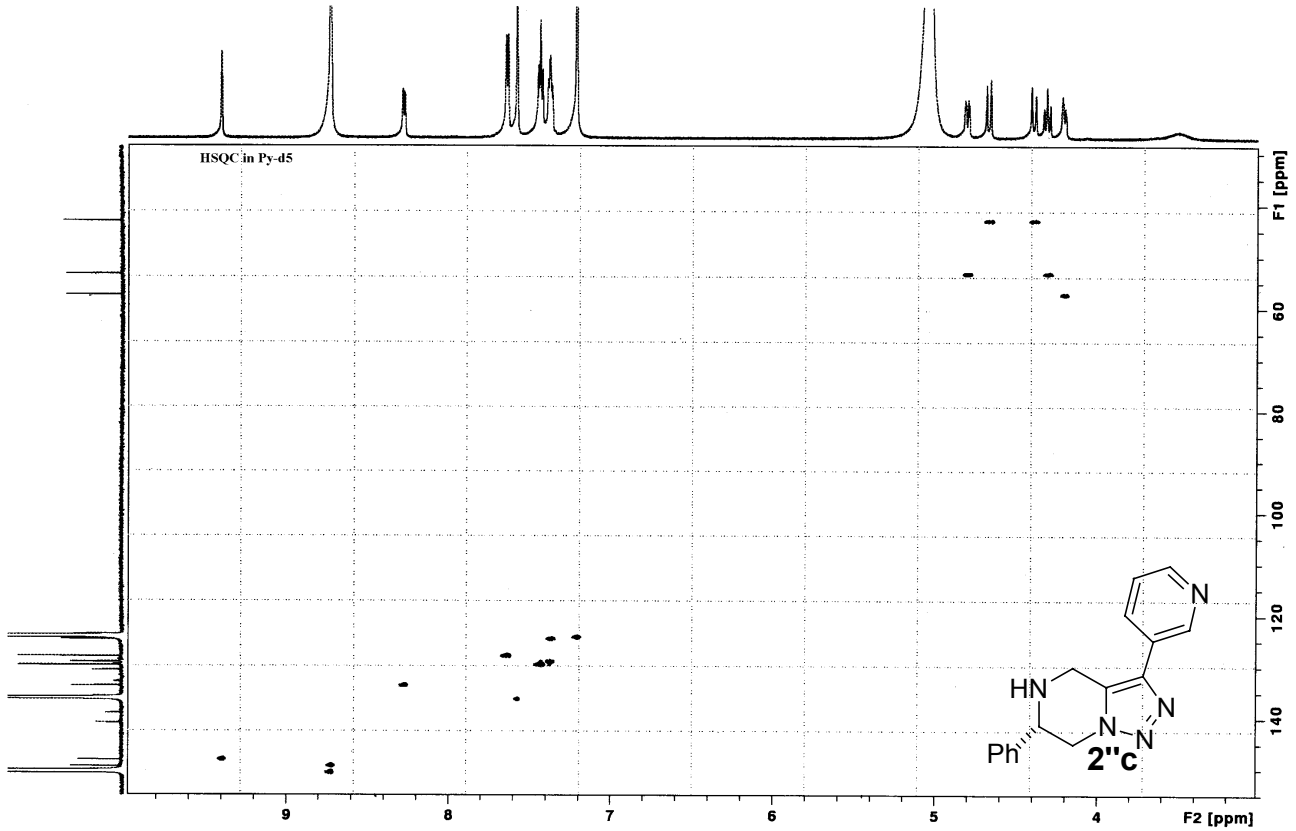
^{13}C NMR spectra of 2″c (150 MHz):



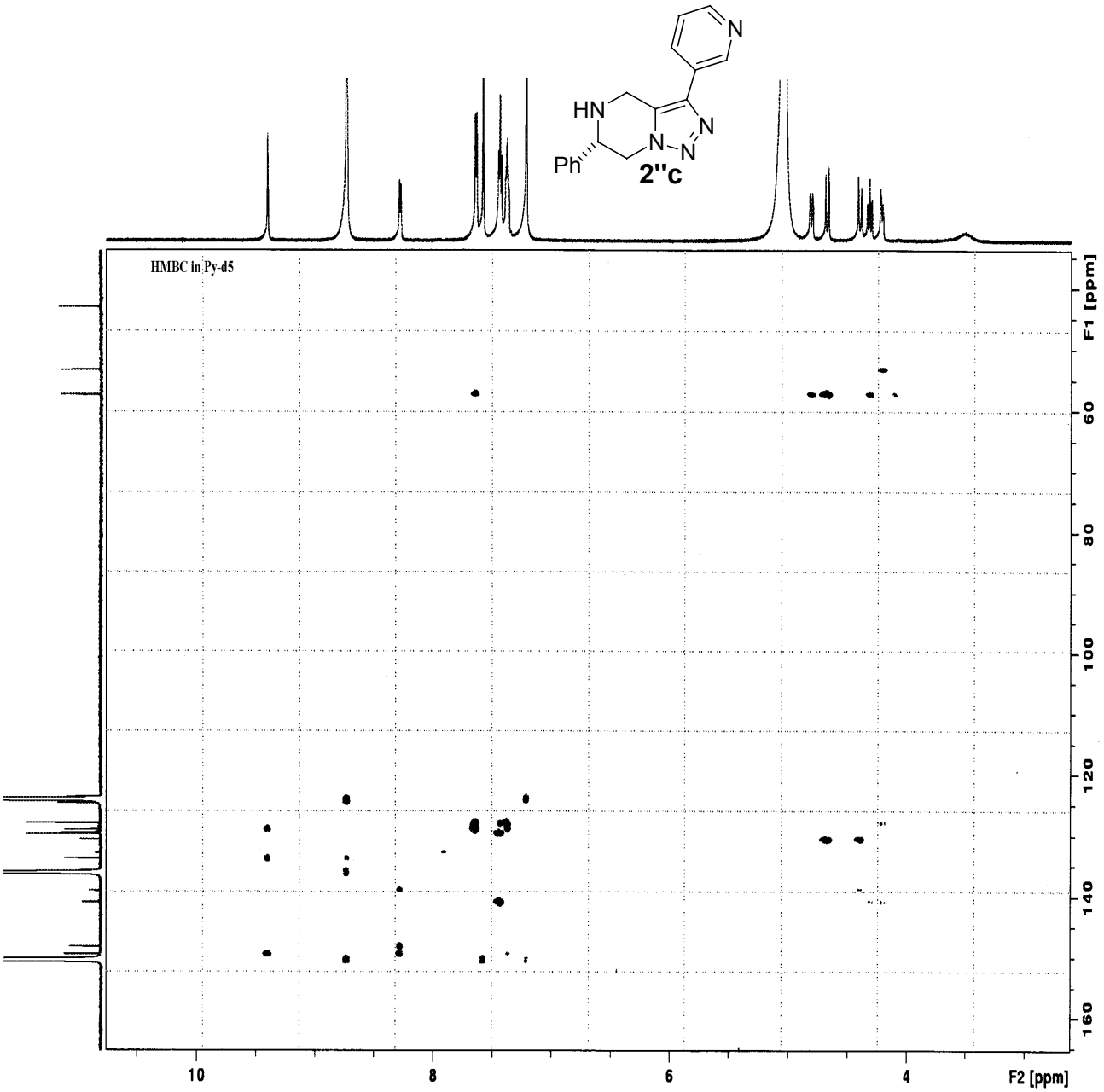
DEPT of 2″c (150 MHz):



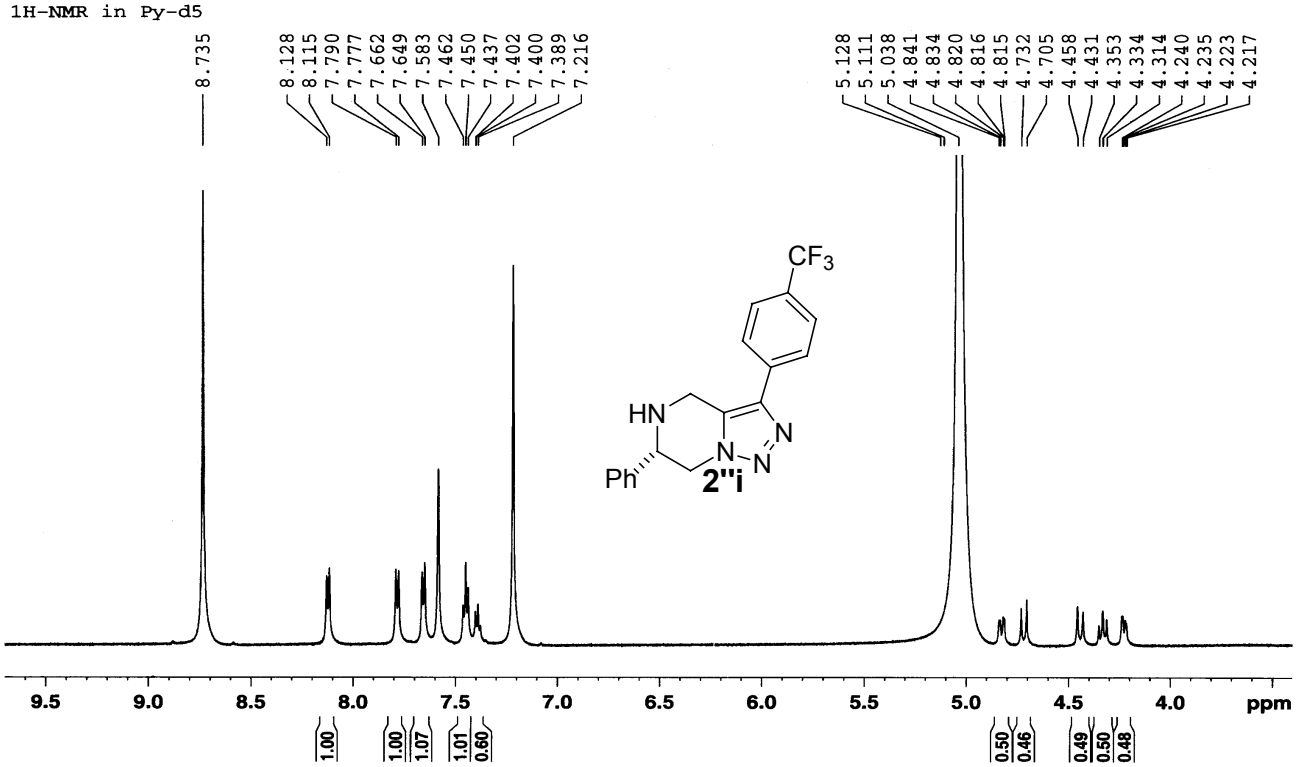
HSQC of 2″c (150 MHz):



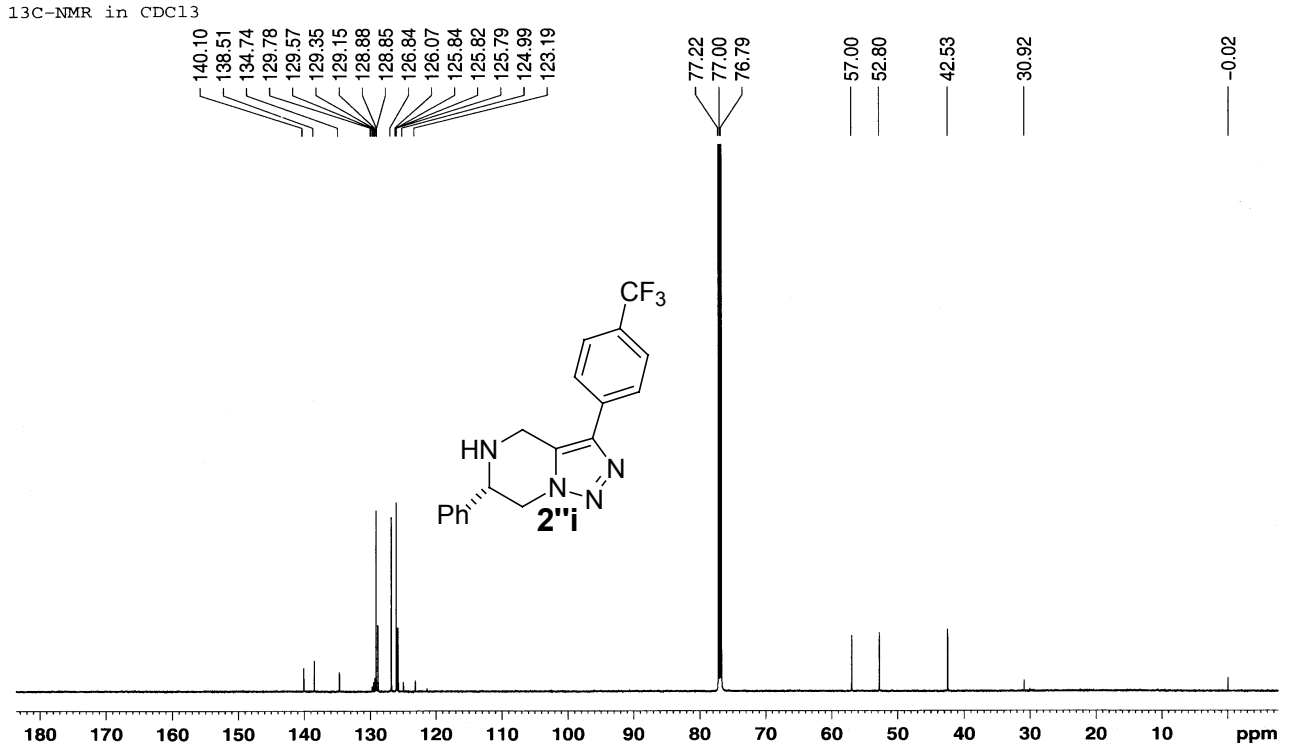
HMBC of 2″c (150 MHz):



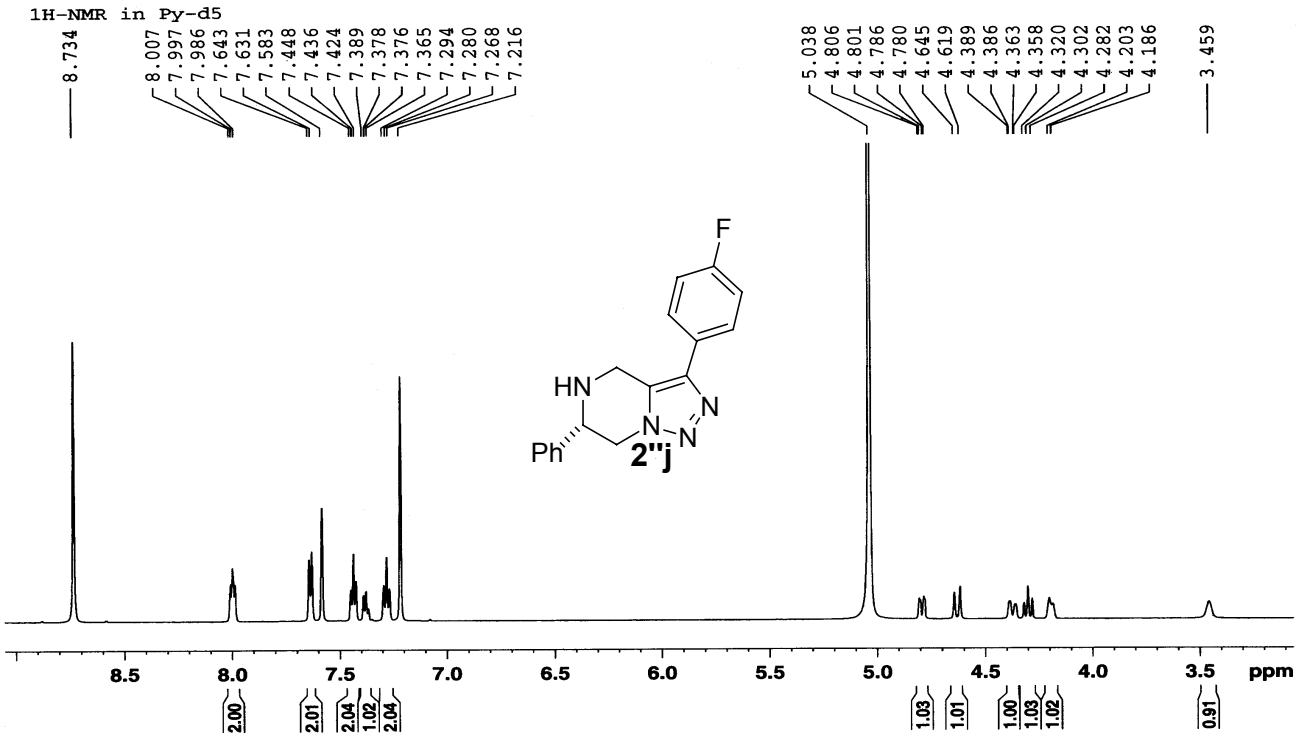
^{1}H NMR spectra of 2″i (600 MHz):



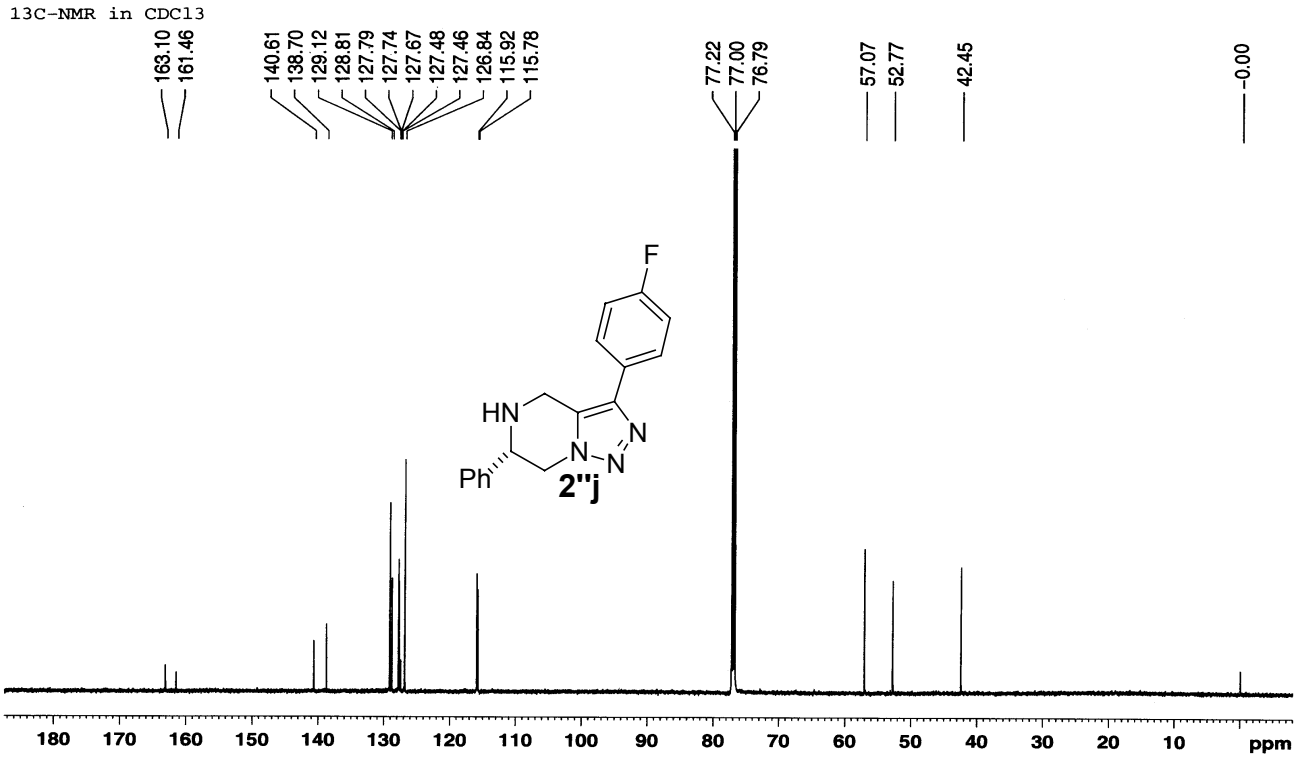
^{13}C NMR spectra of 2″i (150 MHz):



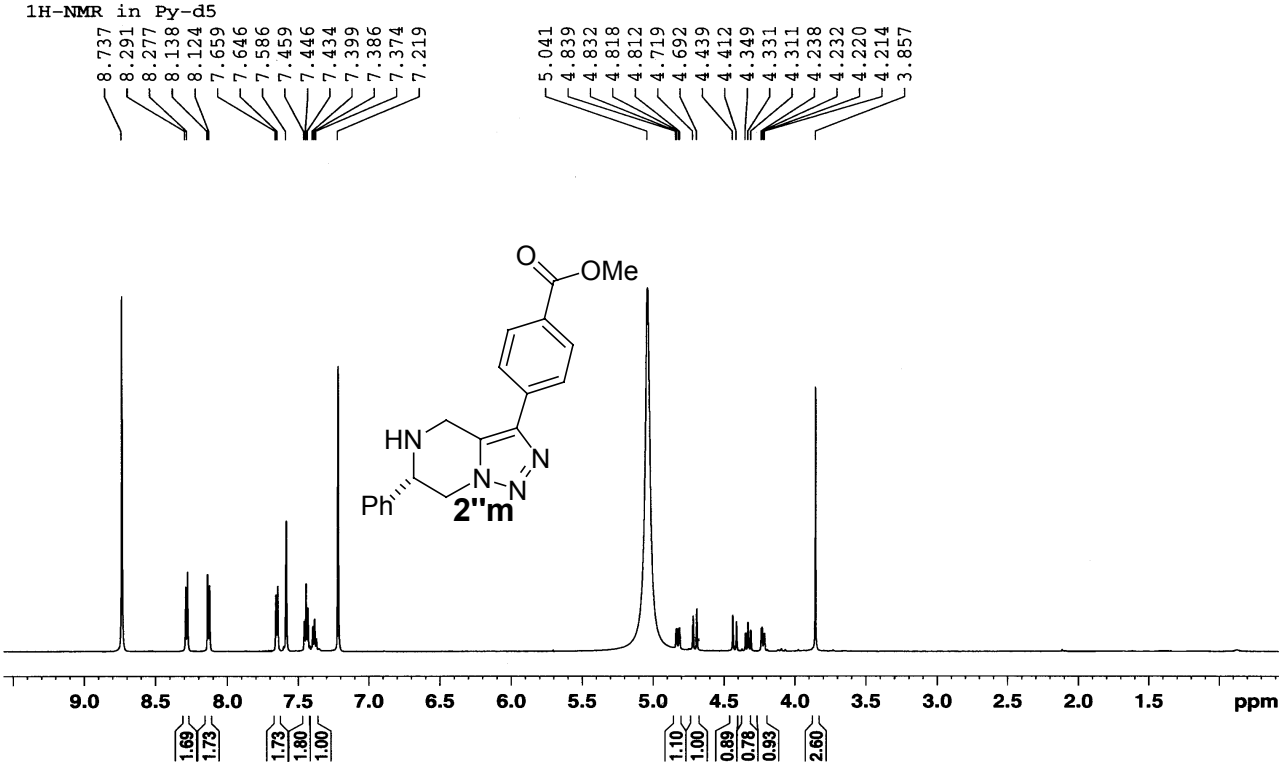
^{1}H NMR spectra of 2″j (600 MHz):



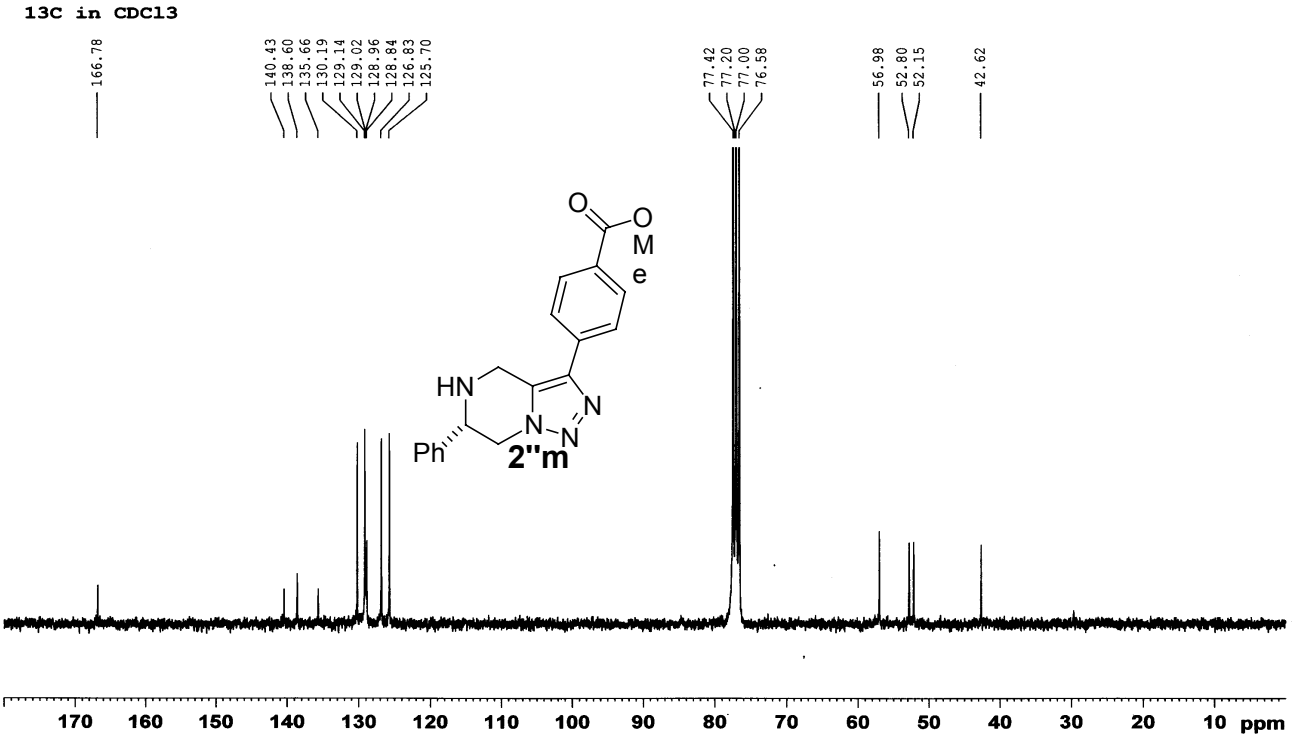
^{13}C NMR spectra of 2″j (150 MHz):



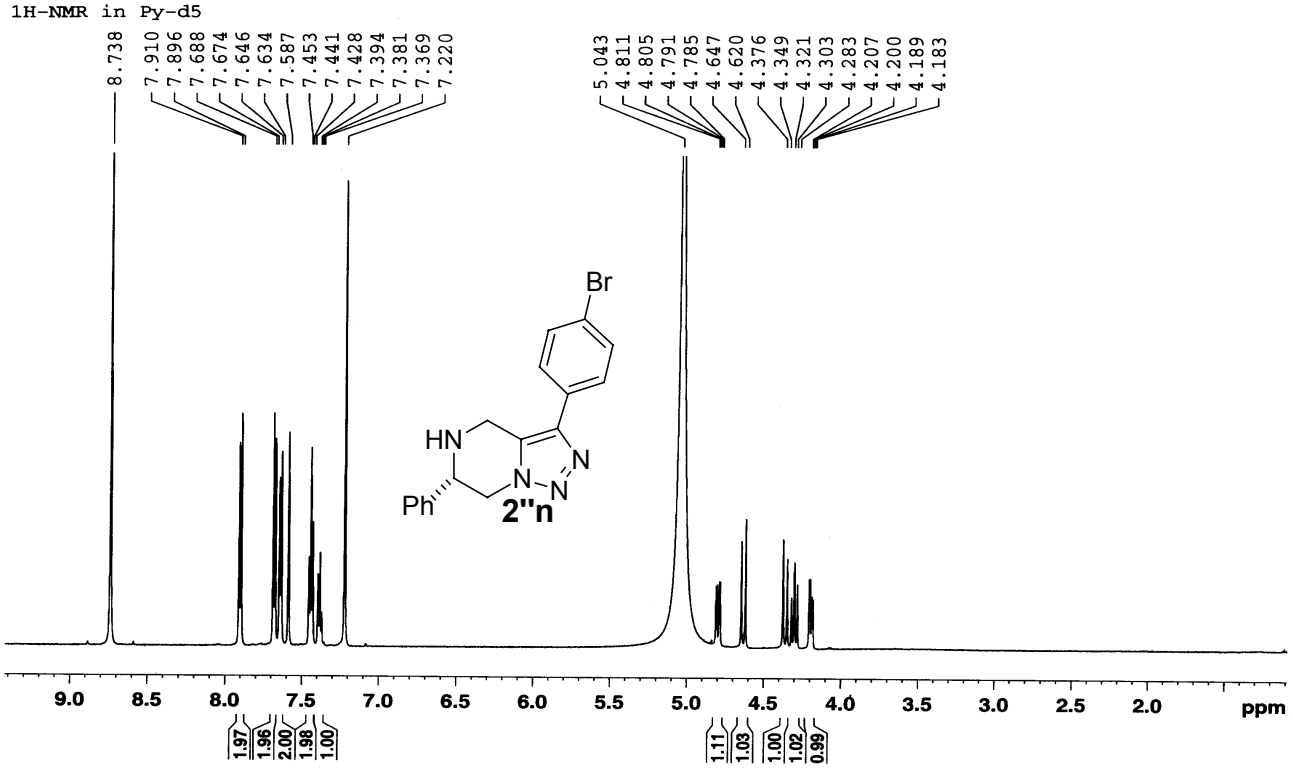
^{1}H NMR spectra of 2″m (600 MHz):



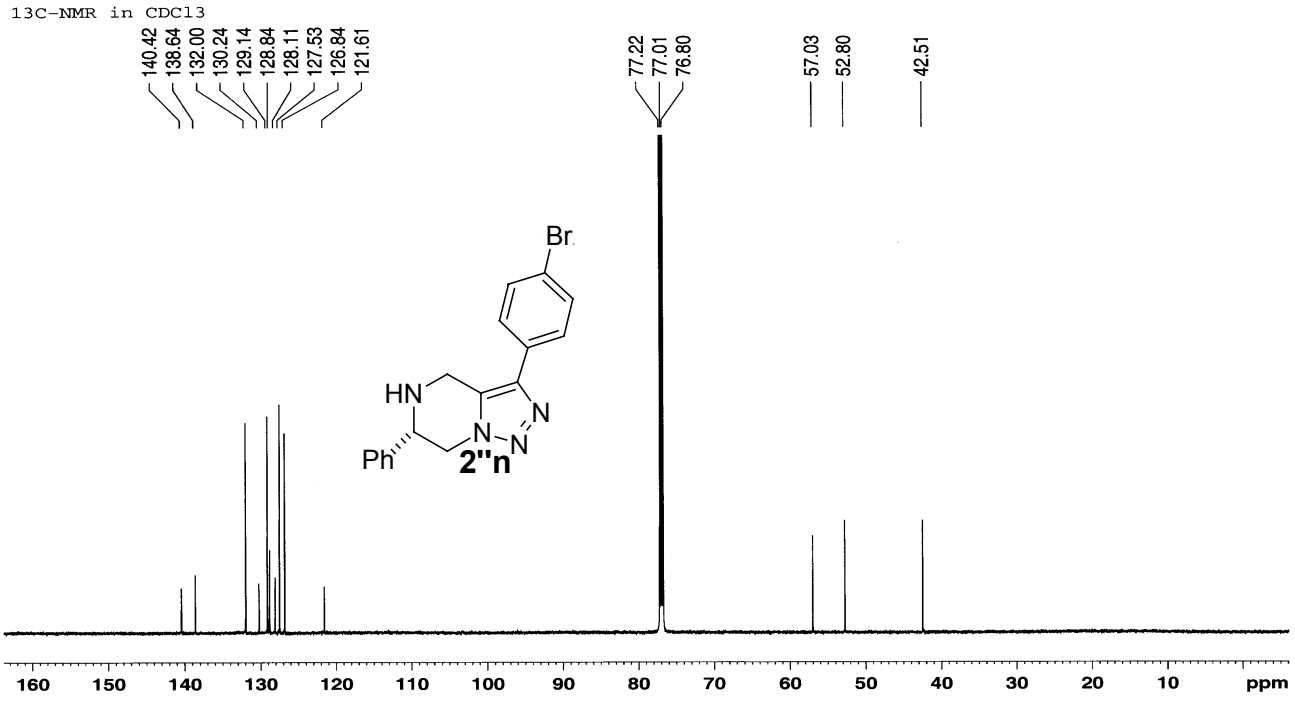
^{13}C NMR spectra of 2″m (75 MHz):



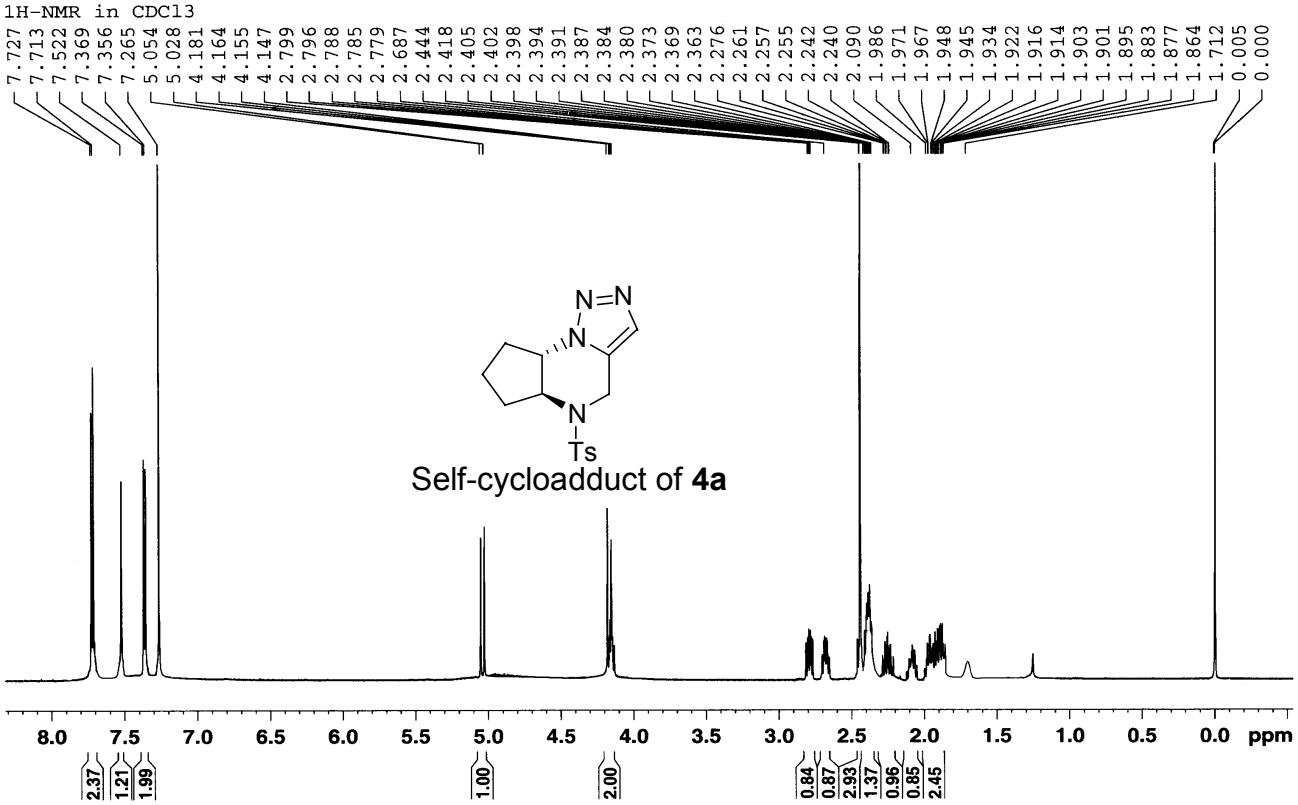
^{1}H NMR spectra of 2″n (600 MHz):



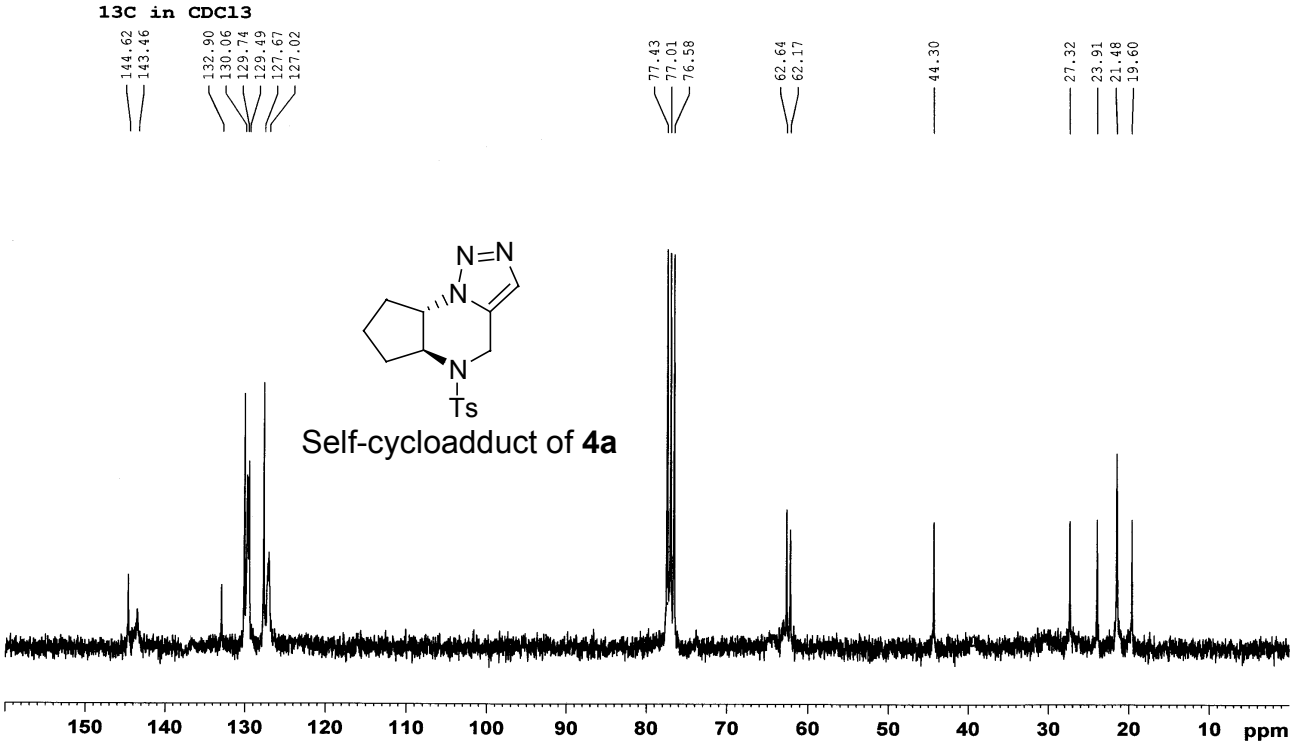
^{13}C NMR spectra of 2″n (150 MHz):



^{1}H NMR spectra of self-cycloadduct of substrate 4a (600 MHz):



^{13}C NMR spectra of self-cycloadduct substrate of 4a (75 MHz):



^{1}H NMR spectra of D (300 MHz):