Supplementary Information for

P450-catalyzed intramolecular sp^3 C—H amination with arylsulfonyl azide substrates

Ritesh Singh, Melanie Bordeaux & Rudi Fasan*

Department of Chemistry, University of Rochester, 14627 Rochester, New York, USA

Correspondence should be addressed to R.F. (fasan@chem.rochester.edu)

Table of contents:

Figure S1: Product distribution for the reactions of FL#62 with substrates **1a-3a** and **4-9**. The bar graph describes the relative amount of the arylsultam and arylsulfonamide products generated in the reactions. Cumulative total turnover numbers (TTN) corresponding to both products are indicated. Reactions conditions: 20 µM FL#62, 10 mM substrate, 5 mM NADPH. Reactions were carried out at room temperature and under argon, stopped after 16 hours, and analyzed by gas chromatography.

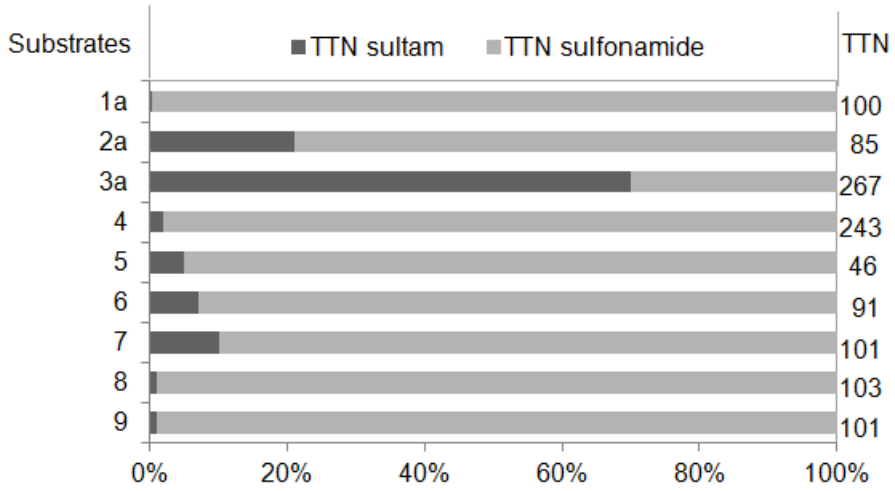


Figure S2: Percentage of C—H amination product (= [arylsultam] / ([arylsultam]+[arylsulfonamide])) from the reactions of $P450_{BM3}$ (=WT), J, 139-3, FL#62 (light blue) and their T268A-containing counterparts (dark blue) with substrate **2a**. Reactions conditions: 20 µM P450, 10 mM substrate, 5 mM NADPH. Reactions were carried out at room temperature and under argon, stopped after 16 hours, and analyzed by gas chromatography.

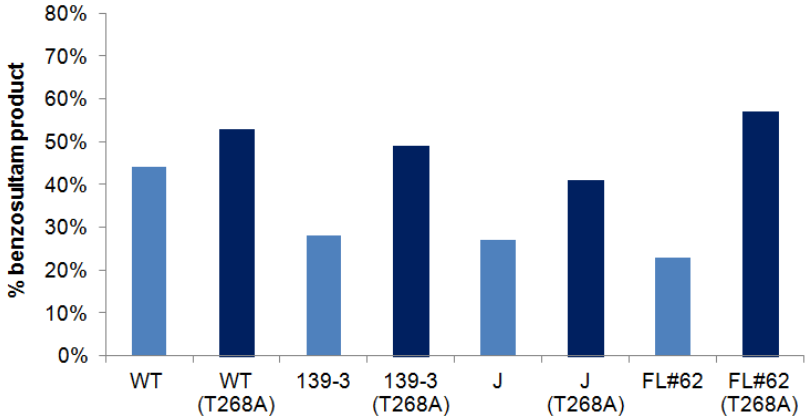


Figure S3. Calibration curves used for the quantification of the benzosultam products by GC-MS (**2b, 8b, 9b**) or GC-FID (**1b, 3b, 4b, 5b, 6b, 7b**). The graphs report the ratio between the peak areas corresponding to the benzosultam product (authentic standard prepared synthetically) and the internal standard (IS) plotted against the benzosultam concentration.

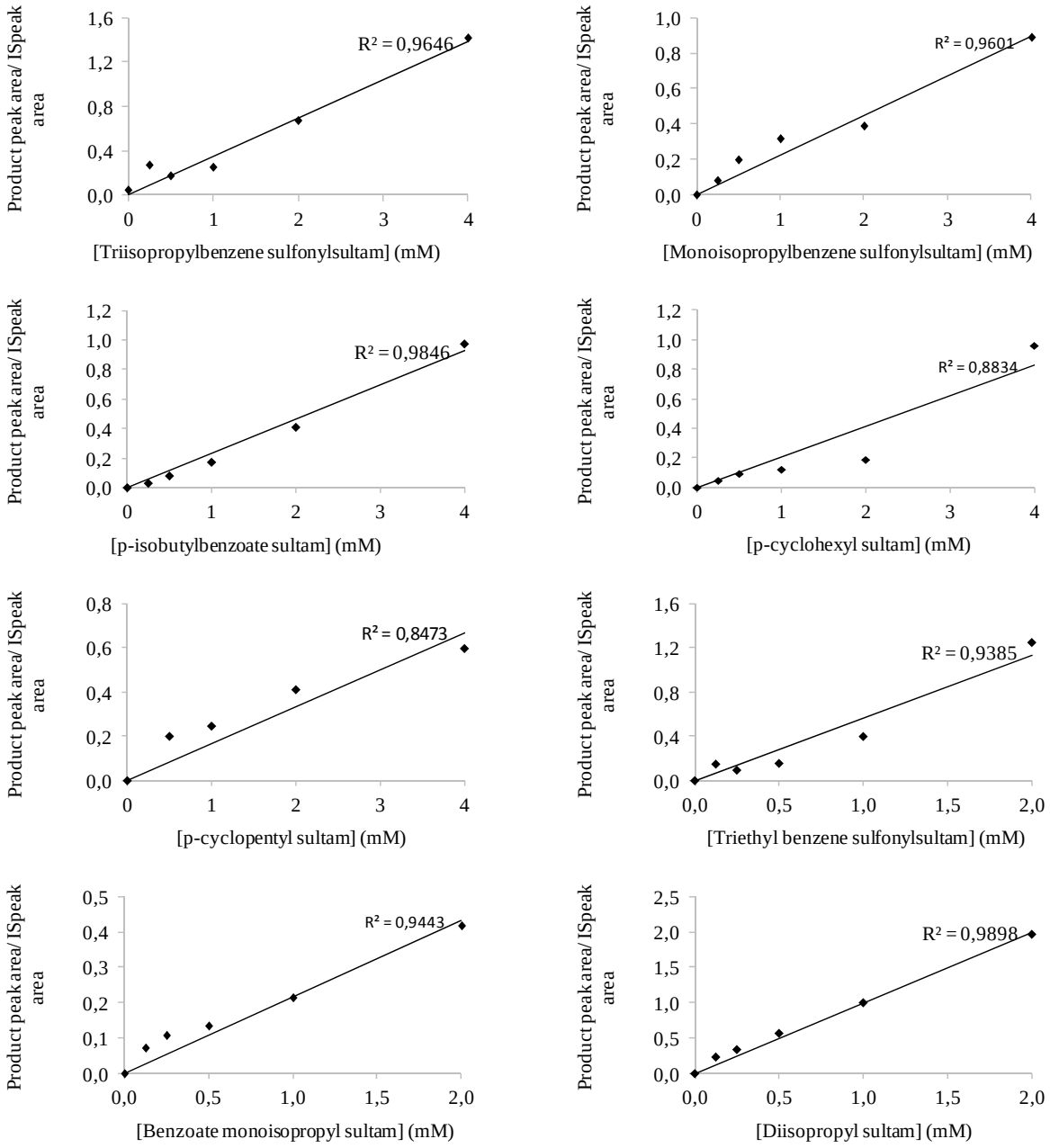
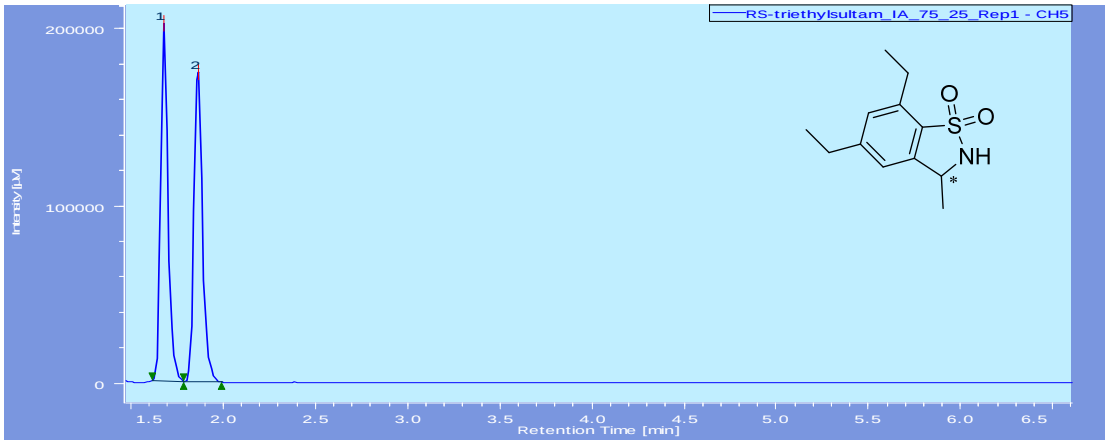


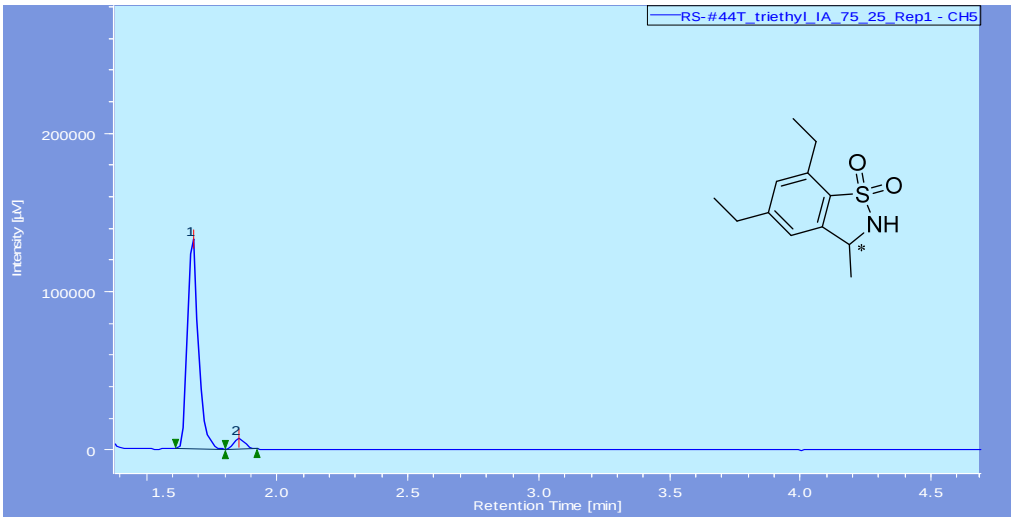
Figure S4. Representative chiral SFC chromatograms corresponding to **2b** as (a) authentic racemic standard and as produced from the reactions with (b) #139-3(T268A)**,** (c) #J(T268A), and (d) $P450_{BM3}$(T268A).

(a) Racemic **2b**:



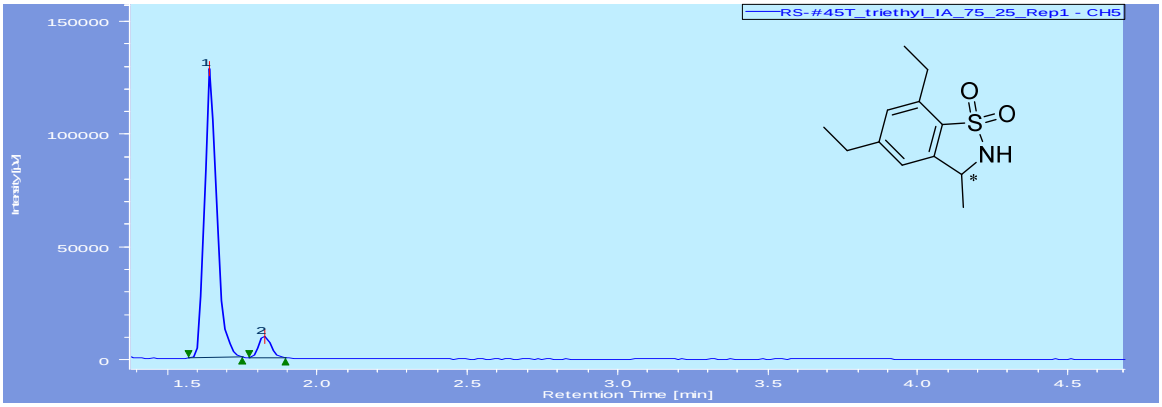
Peak Name	tR	Area%
Enantiomer 1	1.680	50.026
Enantiomer 2	1.867	49.974

(b) #139-3(T268A)**:**



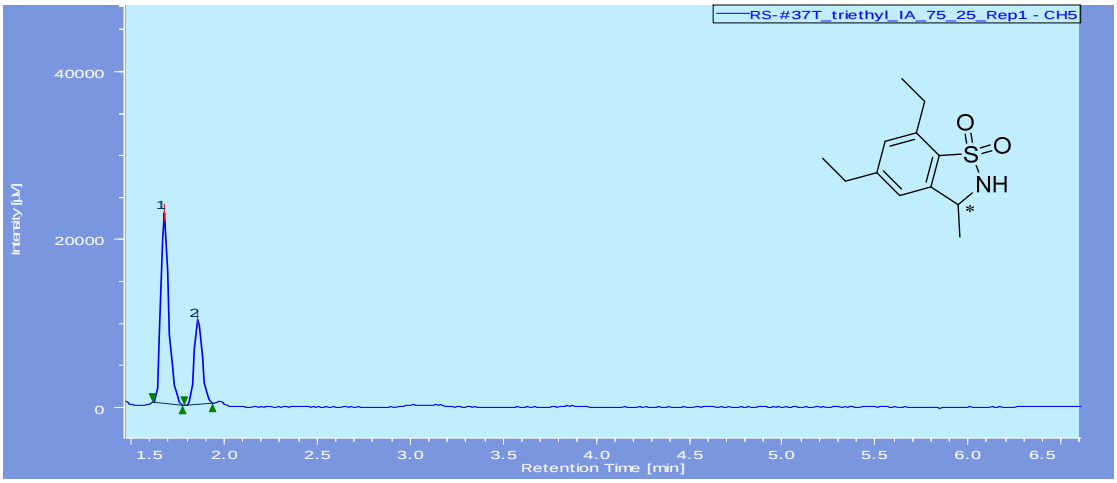
Peak Name	tR	Area%
Enantiomer 1	1.680	95.005
Enantiomer 2	1.853	4.995

(c) #J(T268A):



Peak Name	tR	Area%
Enantiomer 1	1.6400	92.837
Enantiomer 2	1.827	7.163

(d) $P450_{BM3}$(T268A):



Peak Name	tR	Area%
Enantiomer 1	1.680	68.611
Enantiomer 2	1.853	31.389

Table S1. Amino acid mutations in the $P450_{BM3}$ variants investigated in this study. Amino acid residues located within the enzyme active site are underlined.

$P450_{BM3}$ variants	**Amino acid mutations compared to wild-type $P450_{BM3}$**	**Ref.**
$P450_{BM3}$	-	
$P450_{BM3}$(T268A)	T268A	This study
139-3	V78A, H138Y, T175I, V178I, A184V, H236Q, E252G, R255S, A290V, A295T, L353V	[1]
139-3(T268A)	V78A, H138Y, T175I, V178I, A184V, H236Q, E252G, R255S, T268A, A290V, A295T, L353V	This study
J	V78A, T175I, A184V, F205C, S226R, H236Q, E252G, R255S, A290V, L353V	[2]
J(T268A)	V78A, T175I, A184V, F205C, S226R, H236Q, E252G, R255S, T268A, A290V, L353V	This study
FL#62	V78A, F81S, A82V, F87A, P142S, T175I, A180T, A184V, A197V, F205C, S226R, H236Q, E252G, R255S, A290V, L353V	[3]
FL#62(T268A)	V78A, F81S, A82V, F87A, P142S, T175I, A180T, A184V, A197V, F205C, S226R, H236Q, E252G, R255S, T268A, A290V, L353V	This study

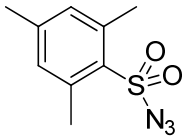
Table S2. C—H amination activity of the $P450_{BM3}$ variants on the arysulfonyl azide substrates **1a-3a** and **4-9**. The table reports the measured total turnover numbers for the formation of the corresponding benzosultam products **1b-9b**. (n.a. = not active).

Catalyst	**Total turnovers (TTN)**								
	1b	**2b**	**3b**	**4b**	**5b**	**6b**	**7b**	**8b**	**9b**
Hemin	n.a.	2	12	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
$P450_{BM3}$	n.a.	5	20	n.a.	18	2	n.a.	n.a.	2
$P450_{BM3}$(T268A)	n.a.	46	20	n.a.	1	4	49	n.a.	1
139-3	n.a.	6	16	n.a.	13	n.a.	20	n.a.	5
139-3(T268A)	n.a.	40	7	n.a.	2	3	4	n.a.	1
J	n.a.	17	51	n.a.	n.a.	3	24	n.a.	1
J(T268A)	n.a.	43	210	n.a.	5	2	44	n.a.	1
FL#62	5	47	388	5	26	13	192	1	1
FL#62(T268A)	n.a.	99	312	n.a.	3	7	21	1	1

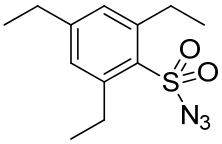
Synthetic Procedures

Chemical synthesis of arylsulfonyl azide substrates.

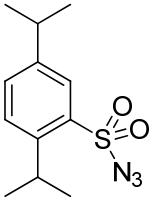
2,4,6-trimethylbenzenesulfonyl azide (**1a**), 2,4,6-triethylbenzenesulfonyl azide (**2a**), and 2,5-diisopropylsulfonyl azide (**5**), were synthesized according to reported procedures.[4] The corresponding spectral data were found to be in agreement with the reported ones.[4]



2,4,6 trimethylbenzenesulfonyl azide (1a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (s, 2H), 2.64 (s, 6H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 139.8, 133.0, 132.0, 22.6, 20.9; LC-MS (ESI) calculated for $C_9H_{12}N_3O_2S$ $[M+H]^+$ *m/z*: 226, Observed: 226.

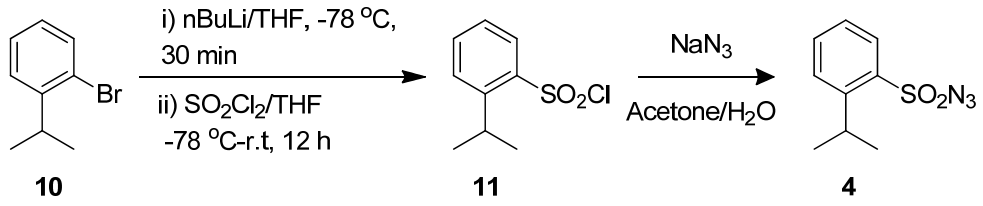


2,4,6 triethylbenzenesulfonyl azide (2a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 2H), 3.06 (q, 4H, *J* = 7.3 Hz), 2.66 (q, 2H, *J* = 7.5 Hz), 1.29 (t, 6H, *J* = 7.4 Hz), 1.26 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 146.3, 132.3, 129.6, 28.5, 28.2, 16.7, 14.7; LC-MS (ESI) calculated for $C_{12}H_{18}N_3O_2S$ $[M+H]^+$ *m/z*: 268, Observed: 268.



2,5 diisopropylbenzenesulfonyl azide (5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89-7.87 (m, 1H), 7.54-7.50 (m, 2H), 3.70 (sep, 1H, *J* = 5.6 Hz), 2.95 (sep, 1H, *J* = 5.7 Hz), 1.30-1.25 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.1, 146.7, 135.6, 133.1, 128.5, 126.7; LC-MS (ESI) calculated for $C_{12}H_{17}N_3NaO_2S$ $[M+Na]^+$ *m/z*: 290, Observed: 290.

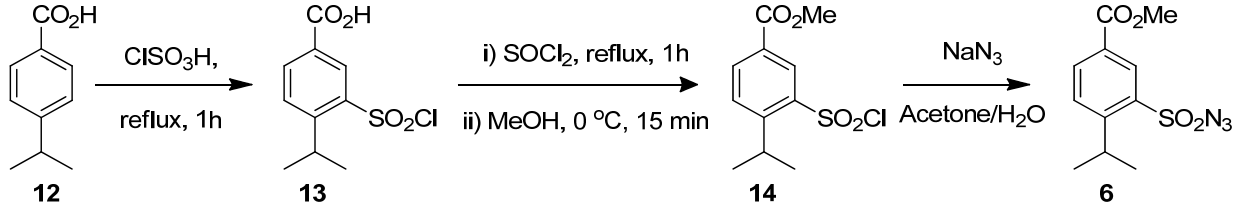
Synthesis of 2-isopropylbenzenesulfonyl azide (4).



To a stirred solution of 1-bromo-2-isopropylbenzene (**10**)[5] (400 mg, 2.0 mmol) in dry THF (4.0 mL) at -78 °C, *n*-butyl lithium (1.6 M in hexane, 0.75 mL, 2.4 mmol) was added slowly and stirred for 30 min, maintaining temperature below -70 °C. Sulfuryl chloride (0.12 mL, 3 mmol) was then added and stirred overnight at room temperature. After the completion of reaction (as observed from TLC), reaction mixture was quenched with water followed by extraction with ether (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under vacuum. Flash column chromatography of the obtained residue on a silica gel furnished 2-isopropylbenenesulfonyl chloride (**11**) in 35% yield as a colorless oil. R_f = 0.88 (1% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05-8.04 (m, 1H), 7.70-7.67 (m, 1H), 7.62-7.60 (m, 1H), 7.39-7.26 (m, 1H), 4.07 (sep, 1H, *J* = 7.6 Hz), 1.35 (d, 6H, *J* = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.3, 142.2, 135.5, 128.9, 128.5, 126.4, 29.1, 23.7.

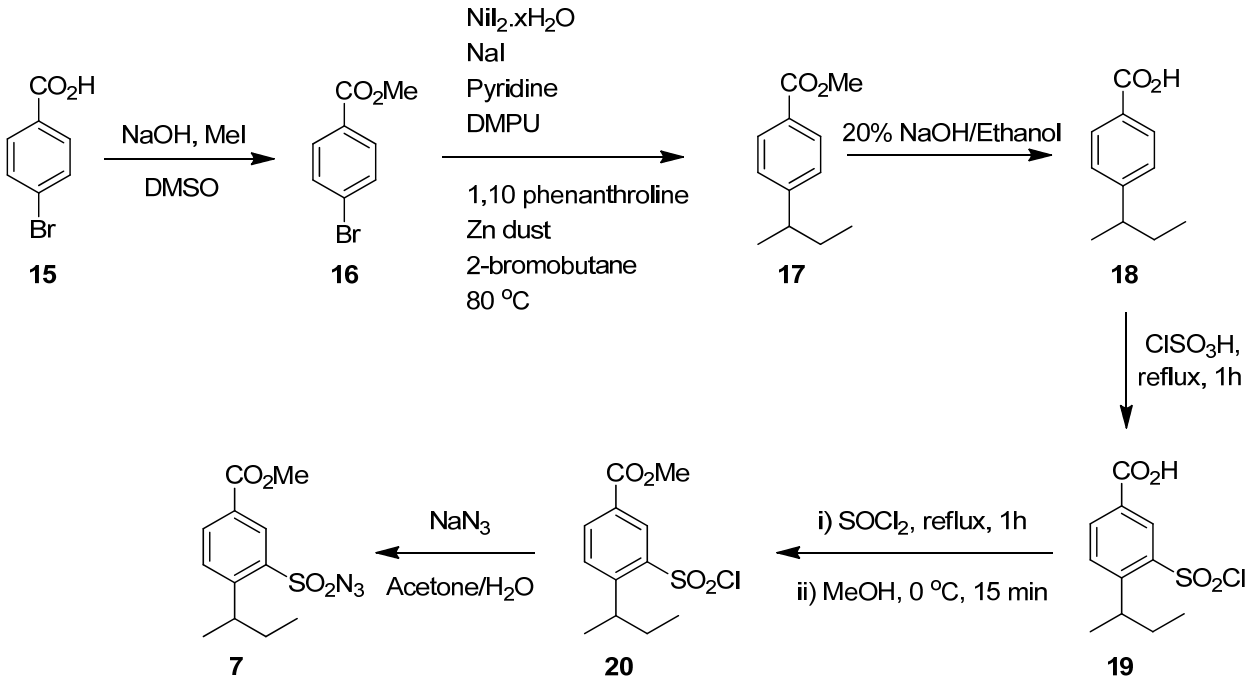
To a stirred solution of **11** (200 mg, 0.91 mmol) in acetone/water (1:1) (3 mL) at 0 °C was added NaN_3 (89 mg, 1.3 mmol) and left stirred at room temperature. After the completion of reaction (as observed from TLC, in about 45 min), reaction mixture was concentrated under vacuum, followed by extraction with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel which furnished 2-isopropylbenzenesulfonyl azide **4** as a colorless oil in 94% yield. R_f = 0.80 (5% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04-8.02 (m, 1H), 7.67-7.64 (m, 1H), 7.59-7.58 (m, 1H), 7.40-7.35 (m, 1H), 3.74 (sep, 1H, *J* = 7.5 Hz), 1.31 (d, 6H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 135.9, 134.9, 129.2, 128.6, 126.3, 29.7, 23.9. LC-MS (ESI) calculated for $C_9H_{11}N_3NaO_2S$ $[M+Na]^+$ *m/z*: 248, Observed: 248.

Synthesis of methyl 3-(azidosulfonyl)-4-isopropylbenzoate (6)



3-(chlorosulfonyl)-4-isopropylbenzoic acid (**13**) was synthesized from commercially available 4-isopropyl benzoic acid (**12**) in 65% yield following a literature procedure.[6] R_f = 0.35 (5% MeOH in $CHCl_3$); ^{1}H NMR (400 MHz, DMSO): δ 11.2 (s, br, 1H), 8.39 (s, 1H), 7.87-7.86 (m, 1H), 7.48-7.47(m, 1H), 4.23 (sep, 1H, *J* = 6.9 Hz), 1.19 (d, 6H, *J* = 6.4 Hz). 3-(chlorosulfonyl)-4-isopropylbenzoic acid (**13**) (0.85 mmol) was refluxed in $SOCl_2$ (1.0 mL) for 1h. The excess $SOCl_2$ was removed under reduced pressure, then methanol (3 mL) was added at 0 ^{o}C, and the solution was stirred for 15 min at room temperature. The solvent was removed under vacuum and the residue obtained was purified by flash chromatography on silica gel which furnished methyl 3-(chlorosulfonyl)-4-isopropylbenzoate (**14**) as pale yellow oil in 86% yield. R_f = 0.75 (10% EtOAc in Hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.26 (d, 1H, *J* = 8.3 Hz), 7.66 (d, 1H, *J* = 8.1 Hz), 4.04 (sep, 1H, *J* = 7.1 Hz), 3.90 (s, 3H), 1.32 (d, 6H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 154.0, 142.3, 135.9, 129.6, 129.4, 128.7, 52.6, 29.4, 23.4. Compound **14** was then converted into methyl 3-(azidosulfonyl)-4-isopropylbenzoate (**6**) in 95% yield, following a procedure identical to that described above for 2-isopropylbenzenesulfonyl azide (**4**). R_f = 0.76 (5% EtOAc in Hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.26 (d, 1H, *J* = 8.2 Hz), 7.66 (d, 1H, *J* = 8.1 Hz), 3.93 (s, 3H), 3.76 (sep, 1H, *J* = 6.9 Hz), 1.30 (d, 6H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 154.5, 136.5, 135.5, 130.3, 129.0, 128.6, 52.6, 30.1, 23.7; LC-MS (ESI) calcultaed for $C_{11}H_{13}N_3NaO_4S$ $[M+Na]^+$ *m/z* 306, Observed: 306.

Synthesis of methyl 3-(azidosulfonyl)-4-sec-butylbenzoate (7)

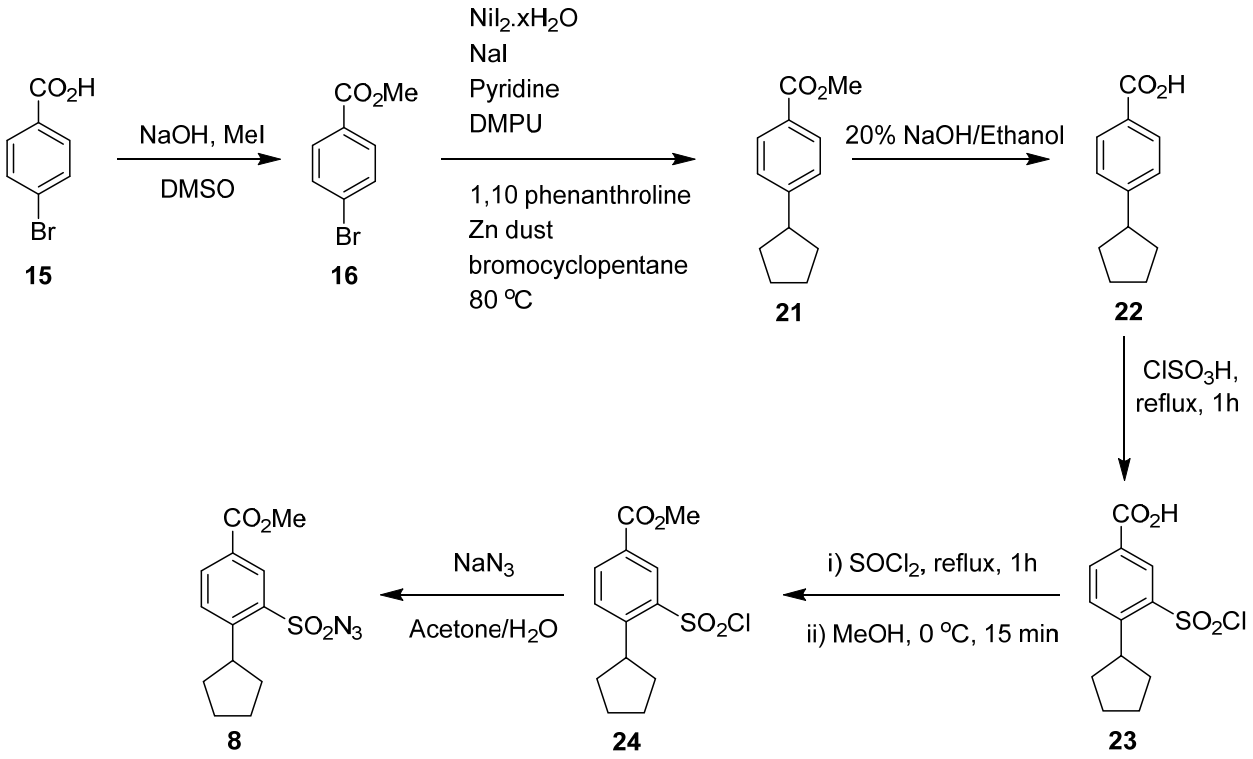


4-bromobenzoate (**16**) was synthesized starting from *p*-bromobenzoic acid (**15**) according to a previously described procedure.[7] *p*-isobutyl methylbenzoate (**17**) was then obtained in 75% yield via nickel-catalyzed reductive coupling of 2-bromobutane with methyl 4-bromobenzoate (**16**) using a procedure reported by Weix and co-workers.[8] R_f = 0.82 (5% ether in pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 2H, *J* = 8.3 Hz), 7.24 (d, 2H, *J* = 8.1 Hz), 3.89 (s, 3H), 2.67-2.63 (m, 1H), 1.62-1.58 (m, 2H), 1.24 (d, 3H, *J* = 7.5 Hz), 0.82-0.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 153.8, 130.1, 127.2, 127.9, 52.1, 41.8, 30.9, 21.6, 12.1; GC-MS m/z (% relative intensity): 192(22.5), 163(100.0), 131(16.3), 91(21.6). After basic hydrolysis (20% NaOH/Ethanol) of **17** to give *p*-isobutylbenzoic acid (**18**) in quantitative yield, the latter was converted to the sulfonyl chloride **19** in 67 % yield. R_f = 0.42 (5% MeOH in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.38 (d, 1H, *J* = 8.2 Hz), 7.69 (d, 1H, *J* = 7.9 Hz), 3.91-3.88 (m, 1H), 1.94-1.72 (m, 2H), 1.35 (d, 3H, *J* = 7.5 Hz), 0.93-0.92 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 154.5, 143.4, 136.3, 130.6, 129.7, 127.7, 36.4, 30.8, 21.7, 12.1.

Methyl 4-(sec-butyl)-3-(chlorosulfonyl)benzoate (**20**) was then synthesized in 86% yield from carboxylic acid **19** according to the procedure described above for methyl 3-(azidosulfonyl)-4-isopropylbenzoate (**6**). R_f = 0.80 (10% EtOAc in Hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.30 (d, 1H, *J* = 8.3 Hz), 7.63 (d, 1H, *J* = 7.9 Hz), 3.95 (s, 3H), 3.75-3.86 (m, 1H), 1.77-1.72 (m, 2H), 1.31 (d, 3H, *J* = 7.3 Hz), 0.91-0.89 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 153.3, 143.1, 135.9, 129.9, 129.4, 128.7, 52.7, 36.3, 30.7, 21.7, 12.1.

Compound **20** was then converted to the desired methyl 3-(azidosulfonyl)-4-sec-butylbenzoate (**7**) in 94% yield following the procedure described above for 2-isopropylbenzenesulfonyl azide (**4**). R_f = 0.79 (10% EtOAc in Hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.26 (d, 1H, *J* = 7.8 Hz), 7.60 (d, 1H, *J* = 7.9 Hz), 3.94 (s, 3H), 3.60-3.54 (m, 1H), 1.76-1.66 (m, 2H), 1.28 (d, 3H, *J* = 7.1 Hz), 0.88-0.85 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 153.7, 137.4, 135.3, 130.4, 129.0, 128.8, 52.4, 36.9, 30.8, 21.8, 11.8; LC-MS (ESI) calcultaed for $C_{11}H_{14}N_3O_4S$ $[M+H]^+$ *m/z* 298, Observed: 298.

Synthesis of methyl 3-(azidosulfonyl)-4-cyclopentylbenzoate (8)



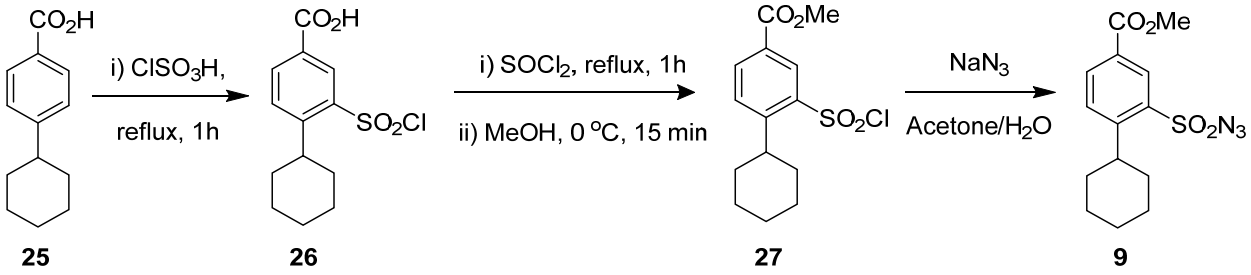
4-bromobenzoate (**16**) was synthesized starting from *p*-bromobenzoic acid (**15**) according to a previously described procedure.[7] *p*-cyclopentyl methylbenzoate (**21**) was then obtained in 75% yield via nickel-catalyzed reductive coupling of bromopentane with methyl 4-bromobenzoate (**16**) using a procedure reported by Weix and co-workers.[8] R_f = 0.85 (5% ether in pentane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, 2H, *J* = 8.3 Hz), 7.28 (d, 2H, *J* = 8.1 Hz), 3.89 (s, 3H), 3.07-3.01 (m, 1H), 2.08 (m, 2H), 1.82-1.59 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 152.2, 129.6, 127.6, 127.1, 51.9, 45.9, 34.5, 25.6; GC-MS m/z (% relative intensity): 204(1.7), 145(6.8), 131(2.6). After basic hydrolysis (20% NaOH/Ethanol) of **21** to give *p*- 4-cyclopentylbenzoic acid (**22**) in quantitative yield, the latter was converted to the sulfonyl chloride **23** in 67 % yield. R_f = 0.42 (5% MeOH in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.36 (d, 1H, *J* = 8.2 Hz), 7.69 (d, 1H, *J* = 8.1 Hz), 4.15-4.11 (m, 1H), 2.25 (m, 2H), 1.87-1.61 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 154.3, 143.4, 136.2, 130.4, 130.3, 127.5, 41.2, 36.2, 26.5.

Methyl 3-(chlorosulfonyl)-4-cyclopentylbenzoate (**24**) was synthesized in 81% yield from carboxylic acid **23** according to the procedure described above for methyl 3-(azidosulfonyl)-4-isopropylbenzoate (**6**). R_f = 0.79 (10% EtOAc in Hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.27 (d, 1H, *J* = 8.3 Hz), 7.66

(d, 1H, *J* = 8.0 Hz), 4.07-4.02 (m, 1H), 3.94 (s, 3H), 2.26-2.25 (m, 2H), 1.90-1.63 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 153.1, 143.1, 135.8, 130.1, 129.6, 128.5, 52.6, 41.1, 36.1, 26.4.

Compound **24** was converted to methyl 3-(azidosulfonyl)-4-cyclopentylbenzoate (**8**) in 95% yield following procedure as described for 2-isopropylbenzenesulfonyl azide (**4**). R_f = 0.79 (10% EtOAc in Hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.25 (d, 1H, *J* = 8.2 Hz), 7.64 (d, 1H, *J* = 8.1 Hz), 3.94 (s, 3H), 3.77-3.73 (m, 1H), 2.19 (m, 2H), 1.88-1.61(m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 153.4, 137.3, 135.4, 130.2, 129.7, 128.3, 52.6, 41.6, 36.2, 26.3; LC-MS (ESI) calculated for $C_{13}H_{16}N_3O_4S$ $[M+H]^+$ *m/z*: 310, Observed 310.

Synthesis of methyl 3-(azidosulfonyl)-4-cyclohexylbenzoate (9)

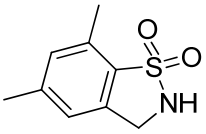


3-(chlorosulfonyl)-4-cyclohexylbenzoic acid (**26**) was synthesized from commercially available 4-cyclohexyl benzoic acid (**25**) in 64% yield following a literature procedure.[8] R_f = 0.37 (5% MeOH in $CHCl_3$); ^{1}H NMR (400 MHz, DMSO): δ 13.2 (s, br, 1H), 8.33 (s, 1H), 7.80-7.78 (m, 1H), 7.39-7.38 (m, 1H), 3.83 (m, 1H), 1.74 (m, 5H), 1.31-1.22 (m, 5H).

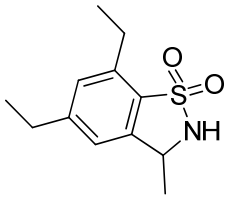
Methyl 3-(chlorosulfonyl)-4-cyclohexylbenzoate (**27**) was obtained in 82% yield from carboxylic acid **26** as pale yellow oil following a procedure identical to that described above for methyl 3-(chlorosulfonyl)-4-isopropylbenzoate (**14**). R_f = 0.77 (10% EtOAc in Hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.30 (d, 1H, *J* = 8.2 Hz), 7.67 (d, 1H, *J* = 8.1 Hz), 3.96 (s, 3H), 3.71 (m, 1H), 1.97-1.82 (m, 5H), 1.50-1.26 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 152.8, 142.6, 135.8, 130.0, 129.8, 128.6, 52.7, 40.1, 33.8, 26.4, 25.9. Compound **27** was then converted into methyl 3-(azidosulfonyl)-4-cyclohexylbenzoate (**9**) in 94% yield, following a procedure identical to that described above for 2-isopropylbenzenesulfonyl azide (**4**). R_f = 0.76 (10% EtOAc in Hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.26 (d, 1H, *J* = 8.2 Hz), 7.64 (d, 1H, *J* = 7.9 Hz), 3.95 (s, 3H), 3.36 (m, 1H), 1.87-1.78 (m, 5H), 1.50-1.24 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 153.3, 136.7, 135.3, 130.4, 129.7, 128.5, 52.6, 40.7, 34.1, 26.5, 25.8; LC-MS (ESI) calculated for $C_{14}H_{17}N_3NaO_4S$ $[M+Na]^+$ *m/z*: 346, Observed: 346.

Chemical synthesis of benzosultam standards

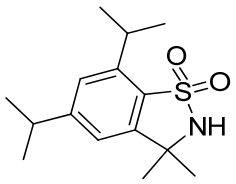
To generate aunthetic stardards for the P450-catalyzed C—H amination reactions, benzosultams **1b**-**9b** were prepared from the respective arylsulfonyl azide substrates using Co-(TPP) catalyst according to previously reported procedures.[4] Briefly, in an oven-dried Schlenk tube, strictly following Schlenk technique, benzenesulfonyl azide (0.2 mmol), catalyst Co-(TPP) (0.004 mmol), and 5Å MS (100 mg) were mixed in toluene (2 mL). After 12-18 hours, the crude products were purified by flash chromatography (25-35% EtOAc in hexane) to give benzosultams **1b**-**9b**.



5,7-dimethyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (1b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (s, 1H), 6.96 (s, 1H), 4.64 (s, 1H), 4.43 (d, 2H, *J* = 5.8 Hz), 2.59 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2, 137.2, 134.1, 131.6, 131.4, 122.2, 45.1, 21.5, 16.9; GC-MS m/z (% relative intensity): 197(100.0), 132(89.2), 182(18.0).

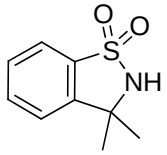


(±)-5,7-diethyl-3-methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (2b). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (s, 1H), 6.97 (s, 1H), 4.98 (s, 1H), 4.69-4.64 (m, 1H), 2.98 (q, 2H, *J* = 7.6 Hz), 2.71 (q, 2H, *J* = 7.4 Hz), 1.55 (d, 3H, *J* = 6.9 Hz,), 1.32 (t, 3H, *J* = 7.4 Hz), 1.23 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.6, 142.5, 140.1, 131.2, 128.6, 120.3, 52.6, 28.9, 24.2, 21.5, 15.3, 14.6; GC-MS m/z (% relative intensity): 239(8.6), 224(100.0), 160(8.5), 144(7.6), 210(4.3).

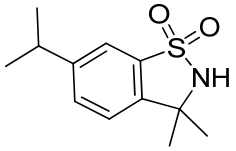


5,7-diisopropyl-3,3-dimethyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (3b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 1H), 6.98 (s, 1H), 4.42 (s, 1H), 3.60 (sep, 1H, *J* = 6.7 Hz), 2.97 (sep, 1H, *J* = 6.7 Hz), 6.2 (s, 6H), 1.34 (d, 6H, *J* = 6.8 Hz), 1.27 (d, 6H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6,

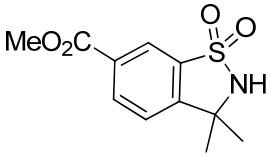
146.7, 145.3, 131.2, 124.4, 117.7, 59.7, 34.6, 29.9, 29.4, 23.9, 23.6; GC-MS m/z (% relative intensity): 182(1.8), 266(100.0), 267(16.7), 268(6.1), 250(1.4), 172(3.4).



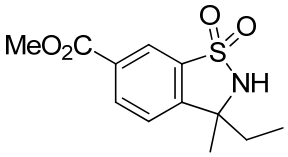
3,3-dimethyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (4b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74-7.73 (m, 1H), 7.64-7.61 (m, 1H), 7.52-7.49 (m, 1H), 7.40-7.38 (m, 1H), 4.66 (s, 1H), 1.66 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 135.2, 133.4, 129.1, 122.8, 121.2, 60.9, 29.7; GC-MS m/z (% relative intensity): 198(1.1), 182(100.0), 117(11.0).



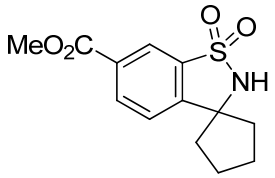
6-isopropyl-3,3-dimethyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (5b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.48 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.0 Hz), 7.28 (d, 1H, J = 7.9 Hz), 4.70 (s, 1H), 3.01 (sep, 1H, J = 7.1 Hz), 1.63 (s, 6H), 1.27 (d, 6H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.6, 143.5, 135.1, 132.1, 122.6, 118.5, 60.6, 33.9, 29.7, 23.7; GC-MS m/z (% relative intensity): 224(100.0), 196(3.3), 182(7.4), 144(17.1), 130(16.8).



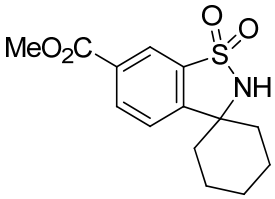
Methyl 3,3-dimethyl-2,3-dihydrobenzo[d]isothiazole-6-carboxylate 1,1-dioxide (6b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.27 (d, 1H, J = 8.2 Hz), 7.46 (d, 1H, J = 8.1 Hz), 4.97 (s, 1H), 3.95 (s, 3H), 1.67 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 150.5, 135.9, 134.5, 131.5, 123.1, 122.9, 60.9, 52.7, 29.4; GC-MS m/z (% relative intensity): 255(2.9), 240(100.0), 241(12.2), 224(5.0), 181(7.0).



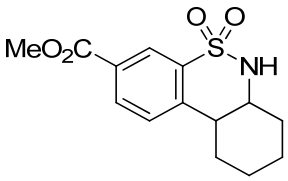
(±)-Methyl 3-ethyl-3-methyl-2,3-dihydrobenzo[d]isothiazole-6-carboxylate 1,1-dioxide (7b). Yield = 96%; R_f = 0.42 (30% EtOAc in Hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.27 (d, 1H, *J* = 8.2 Hz), 7.42 (d, 1H, *J* = 8.1 Hz), 5.08 (s, 1H), 3.96 (s, 3H), 1.93-1.91 (m, 2H), 1.62 (d, 3H, *J* = 7.3 Hz), 0.88-0.85 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 149.1, 136.1, 134.3, 131.5, 123.3, 123.0, 64.5, 52.7, 34.5, 27.6, 8.4; GC-MS m/z (% relative intensity): 270(1.1), 254(6.0), 240(100.0), 238(2.9).



methyl 2H-spiro[benzo[d]isothiazole-3,1'-cyclopentane]-6-carboxylate 1,1-dioxide (8b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.26 (d, 1H, *J* = 8.3 Hz), 7.44 (d, 1H, *J* = 8.1 Hz), 4.88 (s, 1H), 3.95 (s, 3H), 2.17-2.11 (m, 2H), 2.11-2.05 (m, 2H), 1.98 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 149.8, 137.1, 134.3, 131.3, 123.1, 122.6, 71.1, 52.7, 41.6, 24.7; GC-MS m/z (% relative intensity): 281(21.0), 252 (100.0), 266 (8.8), 216(22), 217(25), 202(17.4).



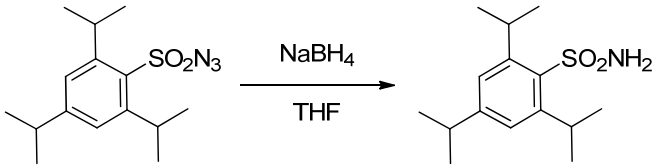
methyl 2H-spiro[benzo[d]isothiazole-3,1'-cyclohexane]-6-carboxylate 1,1-dioxide (9b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.25 (d, 1H, *J* = 8.2 Hz), 7.46 (d, 1H, *J* = 8.1 Hz), 5.12 (s, 1H), 3.94 (s, 3H), 1.87-1.81 (m, 7H), 1.64-1.61 (m, 2H), 1.35-1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 150.6, 136.2, 134.3, 131.5, 123.4, 122.9, 63.9, 52.7, 37.4, 24.7, 22.3; GC-MS m/z (% relative intensity): 295(16.7), 252 (100.0), 231(49.5), 230(26.4), 216(41.5).



methyl 6a,7,8,9,10,10a-hexahydro-6H-dibenzo[c,e][1,2]thiazine-3-carboxylate 5,5-dioxide (9bb). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.11 (d, 1H, *J* = 8.2 Hz), 7.48 (d, 1H, *J* = 8.1 Hz), 4.54 (d, 1H, *J* = 14.6 Hz), 3.93 (s, 3H), 3.57-3.46 (m, 1H), 2.75-2.69 (m, 1H), 2.55-2.52 (m, 1H), 2.17-2.14 (m, 1H),

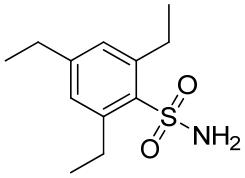
1.94 (m, 2H), 1.51-1.20 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 143.3, 138.4, 132.8, 129.4, 126.6, 125.7, 57.5, 52.5, 42.7, 33.5, 29.2, 25.6, 25.0; GC-MS m/z (% relative intensity): 295(100.0), 264(8.9), 252(38.2), 231(11.1), 216(13.2), 188(25.8). This product was formed in minor amount along with the five-membered major product **9b**.

General procedure for the synthesis of representative arylsulfonamide standards



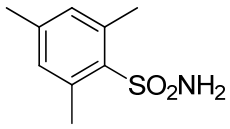
3 **3c**

To a stirred solution of 2,4,6 triisopropylbenzenesulfonyl azide (**3a**) (0.161 mmol) in anhydrous THF (2mL) at 0 ^{o}C was added sodium borohydride (0.162 mmol). After the completion of reaction (30 min) as observed from TLC, the reaction mixture was poured into a 10% HCl solution, and extracted with diethylether (10 x 3 mL). The combined organic layers were then washed with brine, dried over Na_2SO_4 and concentrated under vacuum. Flash column chromatography of the obtained residue on silica gel furnished 2,4,6-triisopropylbenzenesulfonamide (**3c**) as white solid in 86% yield. R_f = 0.56 (35% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17-7.16 (m, 2H), 5.03 (s, 1H), 4.11 (sep, 2H, *J* = 5.3 Hz), 2.90 (sep, 1H, *J* = 5.5 Hz), 1.29-1.24 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.7, 149.1, 134.9, 123.6, 34.2, 29.8, 24.7, 23.6; LC-MS(APCI) m/z: 282 $[M-H]^+$, 267$[M-CH_4]^+$.



2c

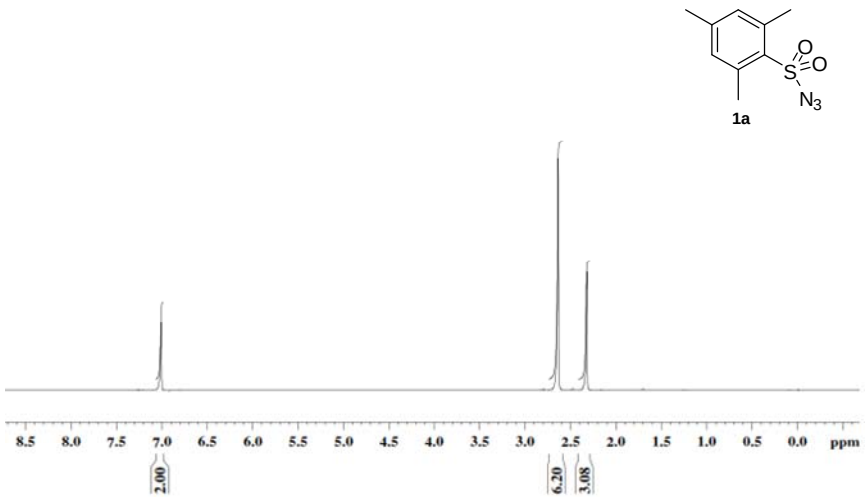
2,4,6-triethylbenzenesulfonamide (2c). Following the same procedure described above for **3a**, 2,4,6 triethylbenzenesulfonyl azide (**2a**) (0.187 mmol), $NaBH_4$ (0.188 mmol), in THF (2 mL) furnished compound **2c** as white solid in 88% yield. R_f = 0.57 (35% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (s, 2H), 5.03 (s, 2H), 3.05 (q, 4H, *J* = 7.4 Hz), 2.60 (q, 2H, *J* = 7.4 Hz), 1.27 (t, 6H, *J* = 7.3 Hz), 1.23 (t, 3H, *J* = 7.6 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 144.5, 135.4, 129.2, 28.4, 28.3, 16.6, 14.9; LC-MS(APCI) m/z: 240$[M-H]^+$.



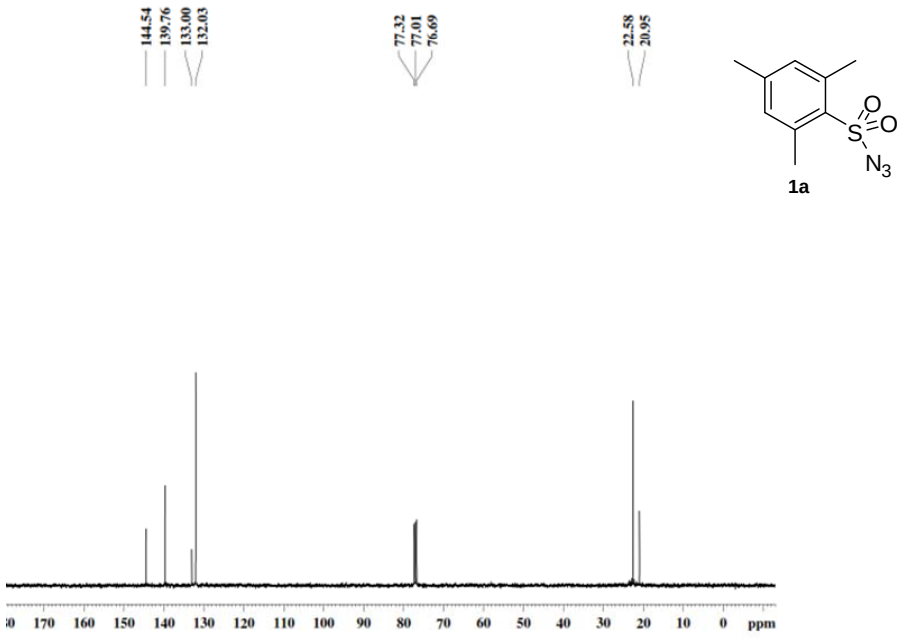
1c

2,4,6-trimethylbenzenesulfonamide (1c). Following similar procedure as described for **3a**, 2,4,6 trimethylbenzenesulfonyl azide (**1a**) (0.187 mmol), $NaBH_4$ (0.188 mmol), in THF (2 mL) furnished compound **1c** as white solid in 85% yield. R_f = 0.52 (35% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (s, 2H), 4.79 (s, 2H), 2.65 (s, 6H), 2.30 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2, 138.2, 135.9, 131.9, 22.9, 20.9; LC-MS(APCI) m/z: 98$[M-H]^+$.

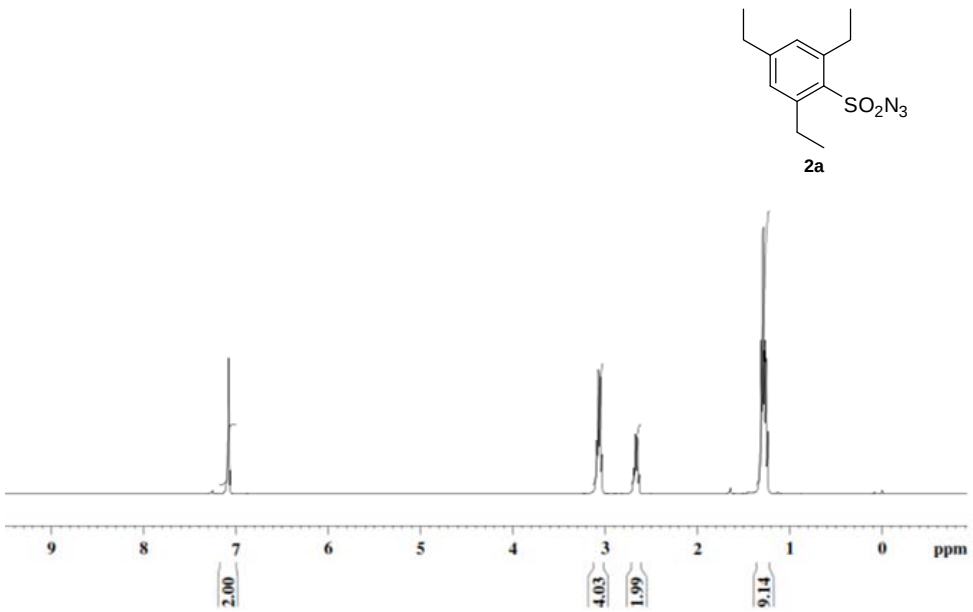
Spectral Data



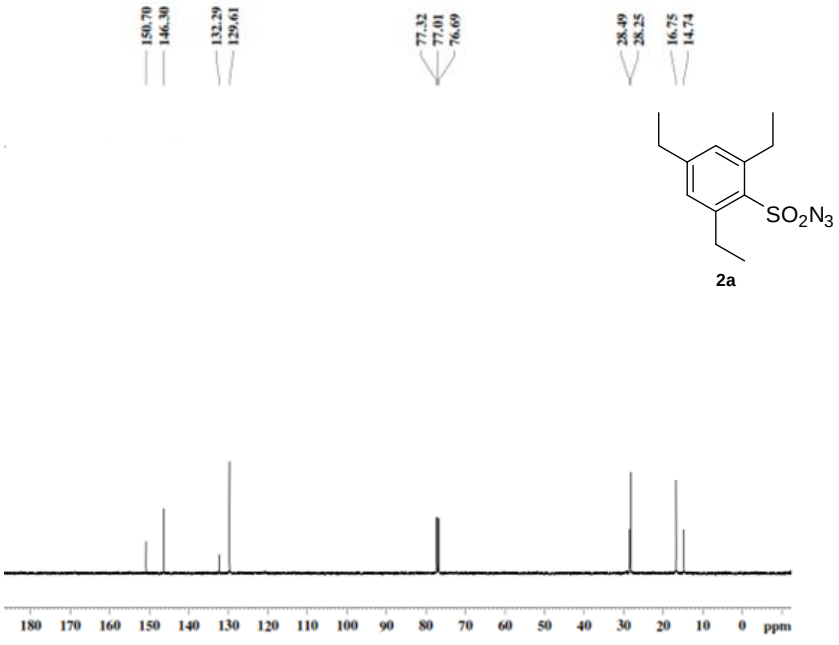
^{1}H NMR($CDCl_3$) of **1**



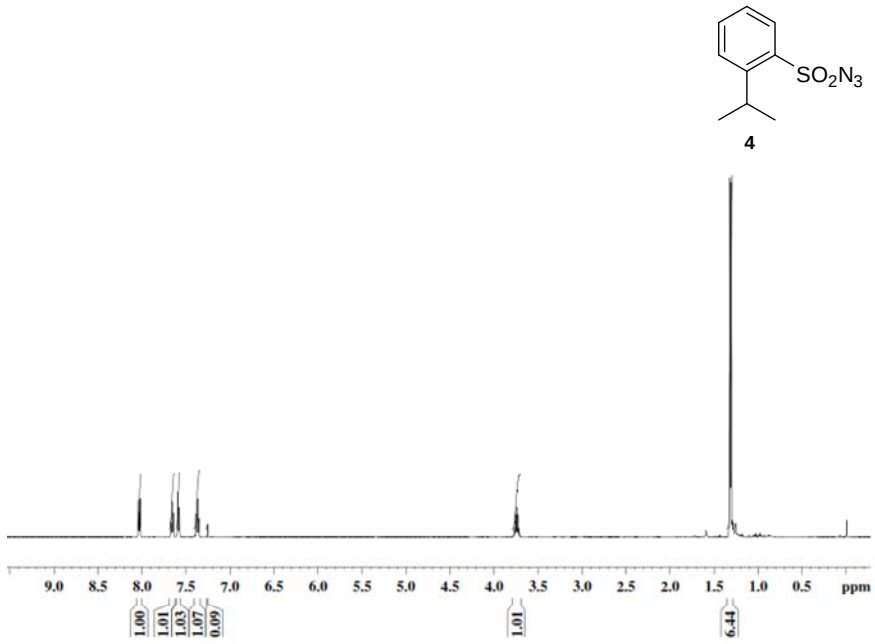
^{13}C NMR($CDCl_3$) of **1**



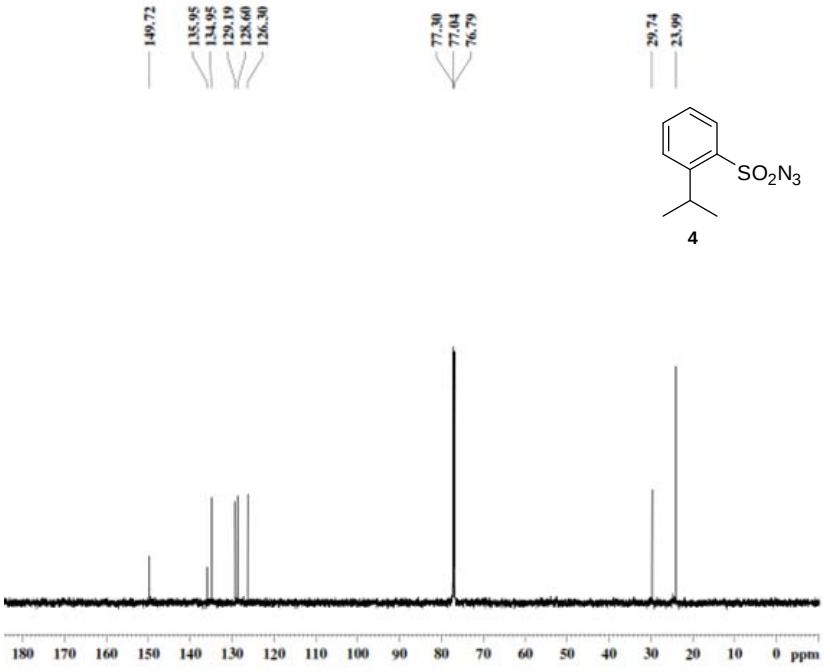
^{1}H NMR($CDCl_3$) of **2**



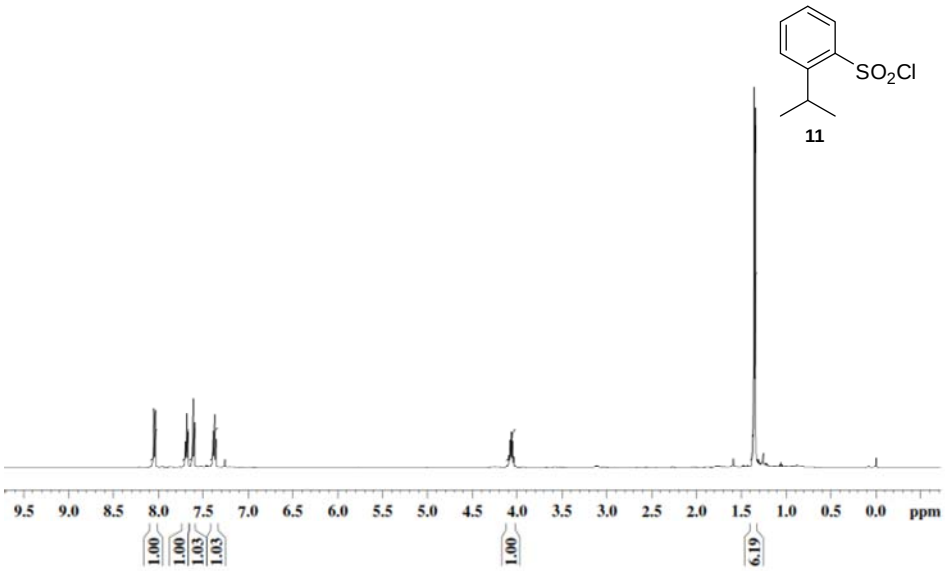
^{13}C NMR($CDCl_3$) of **2**



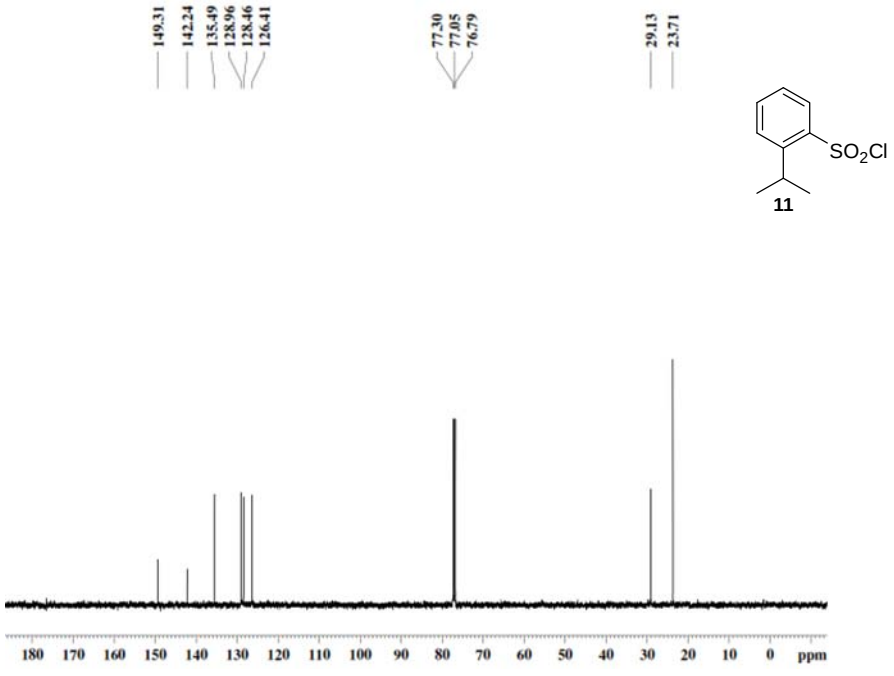
^{1}H NMR($CDCl_3$) of **4**



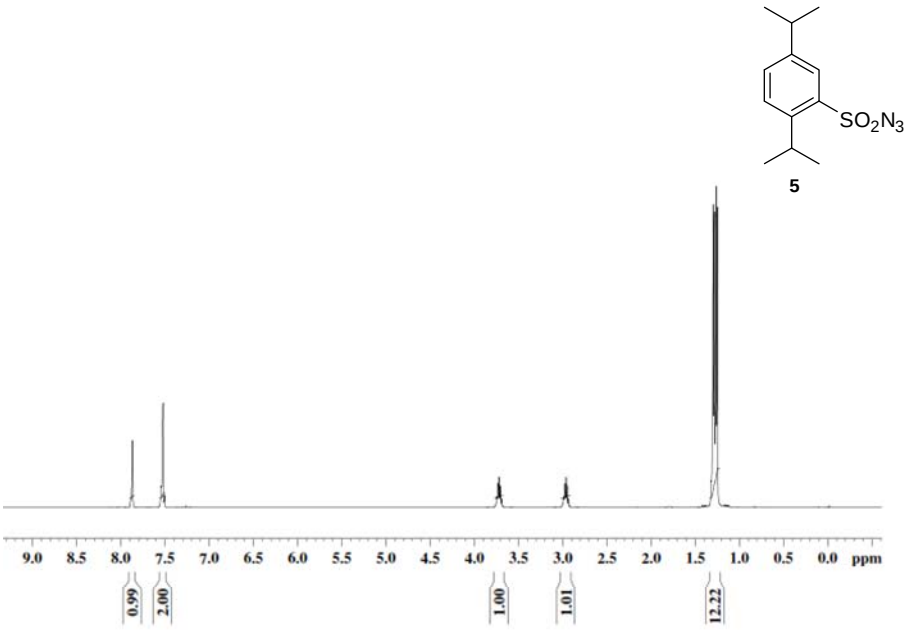
^{13}C NMR($CDCl_3$) of **4**



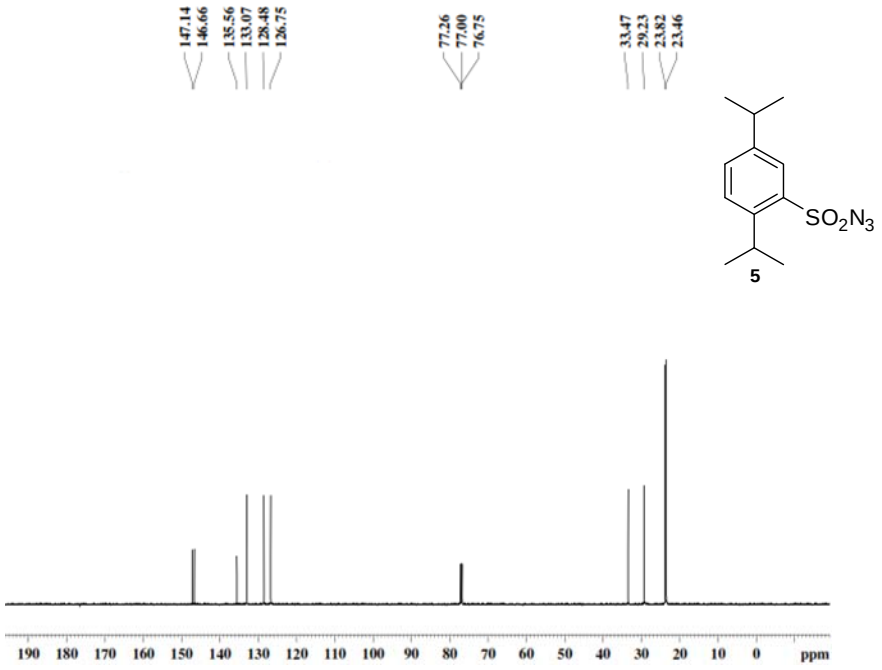
^{1}H NMR($CDCl_3$) of **11**



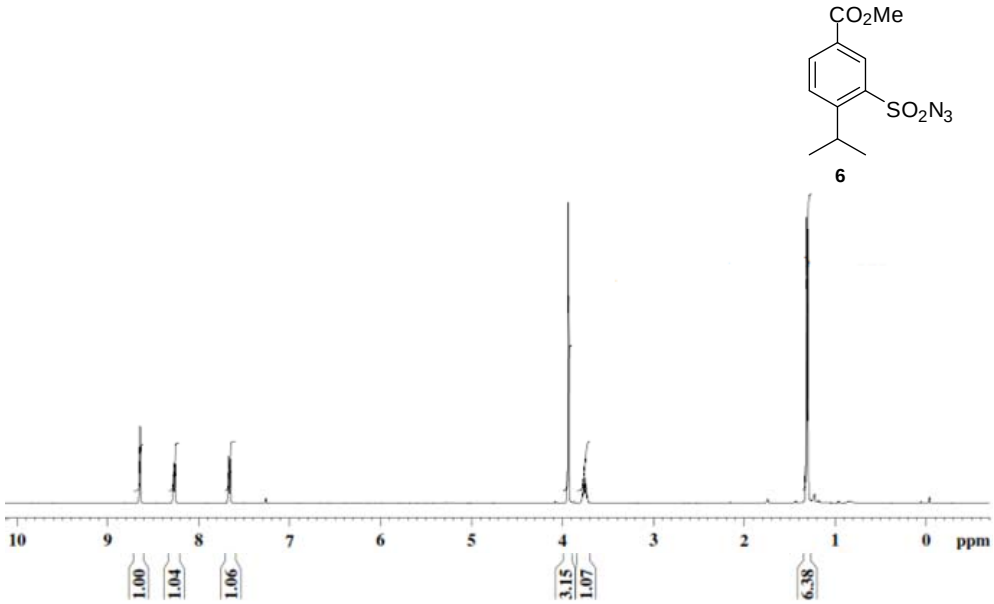
^{13}C NMR($CDCl_3$) of **11**



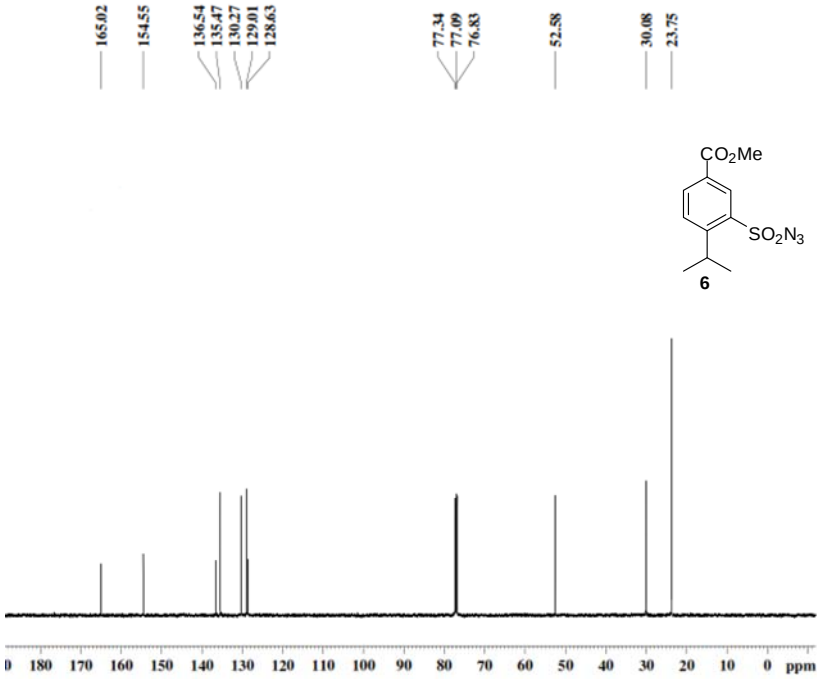
^{1}H NMR($CDCl_3$) of **5**



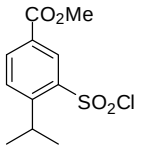
^{13}C NMR($CDCl_3$) of **5**



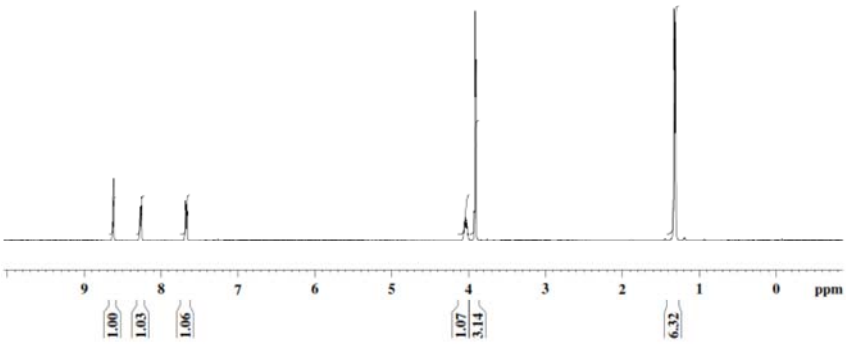
^{1}H NMR($CDCl_3$) of **6**



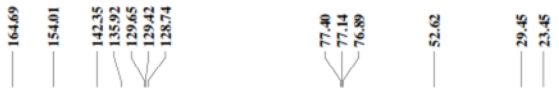
^{13}C NMR($CDCl_3$) of **6**

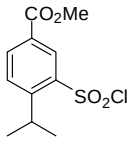


14

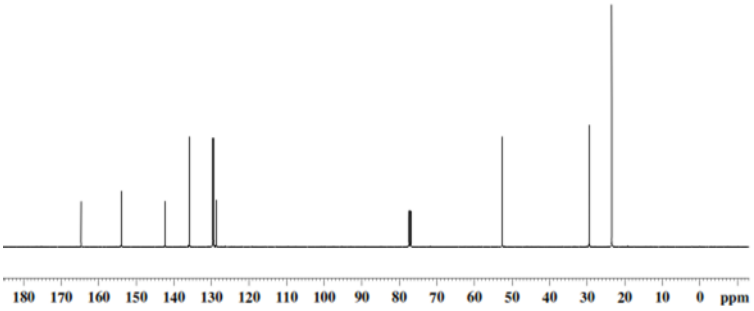


^{1}H NMR($CDCl_3$) of **14**

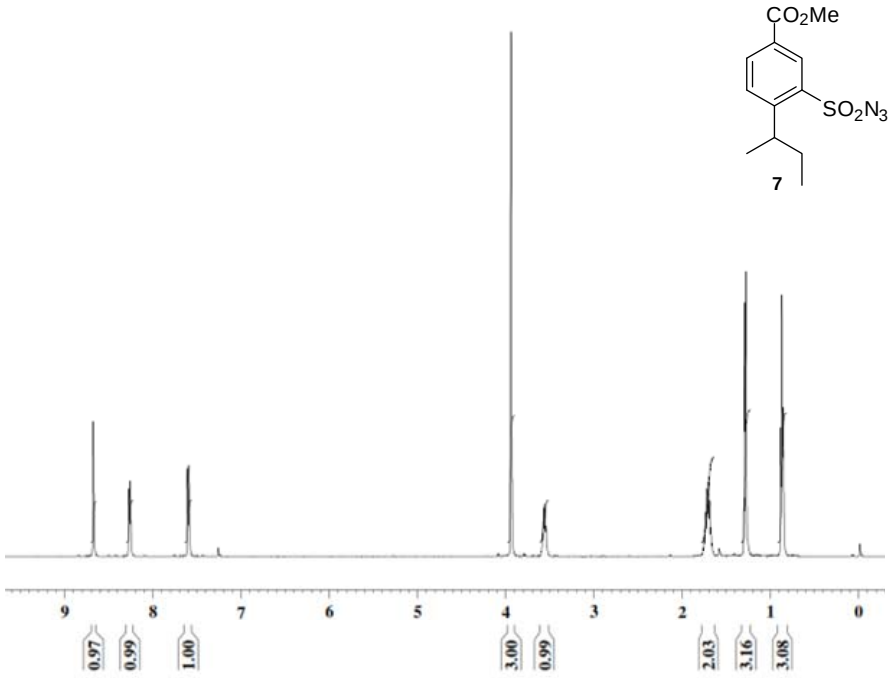




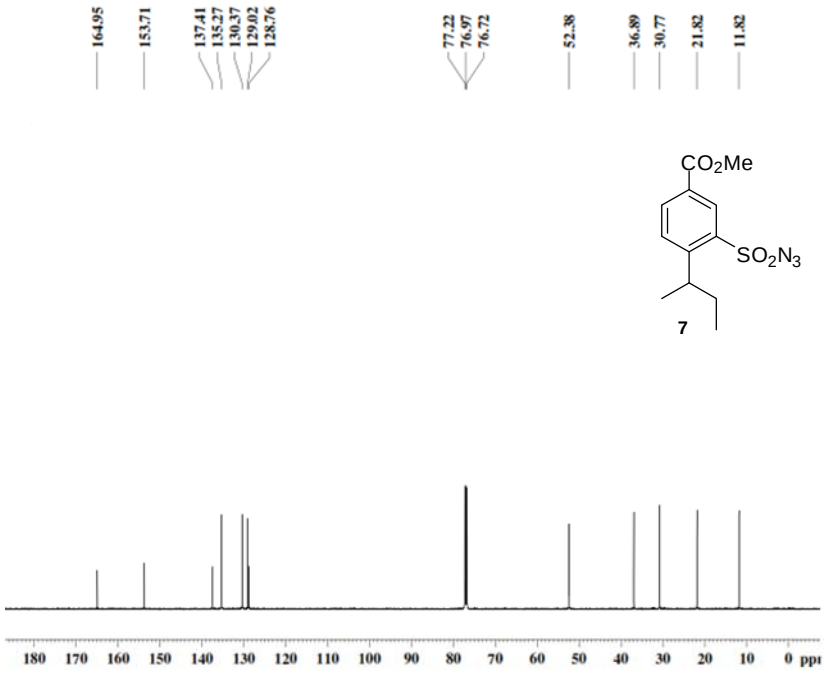
14



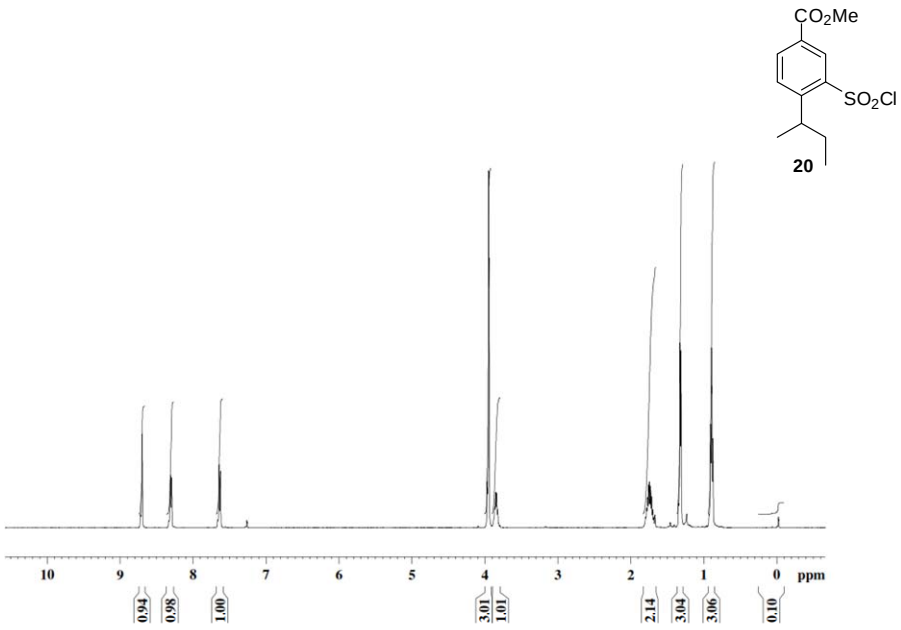
^{13}C NMR($CDCl_3$) of **14**



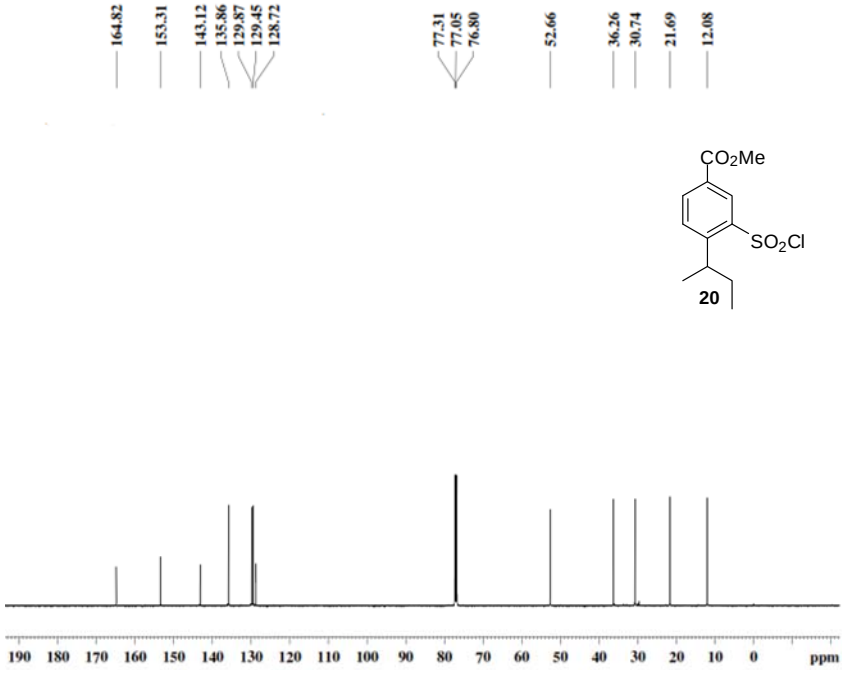
^{1}H NMR($CDCl_3$) of **7**



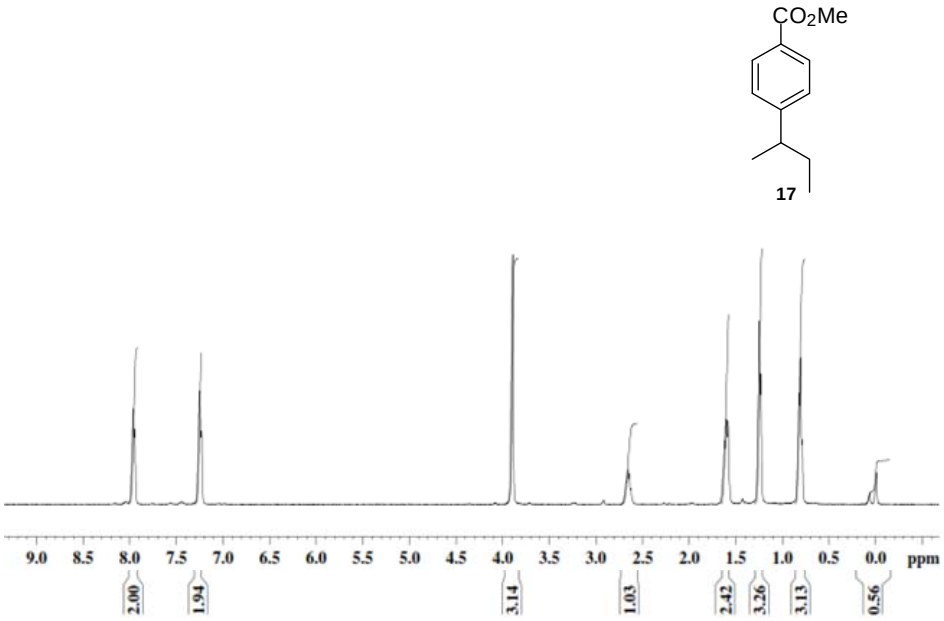
^{13}C NMR($CDCl_3$) of **7**



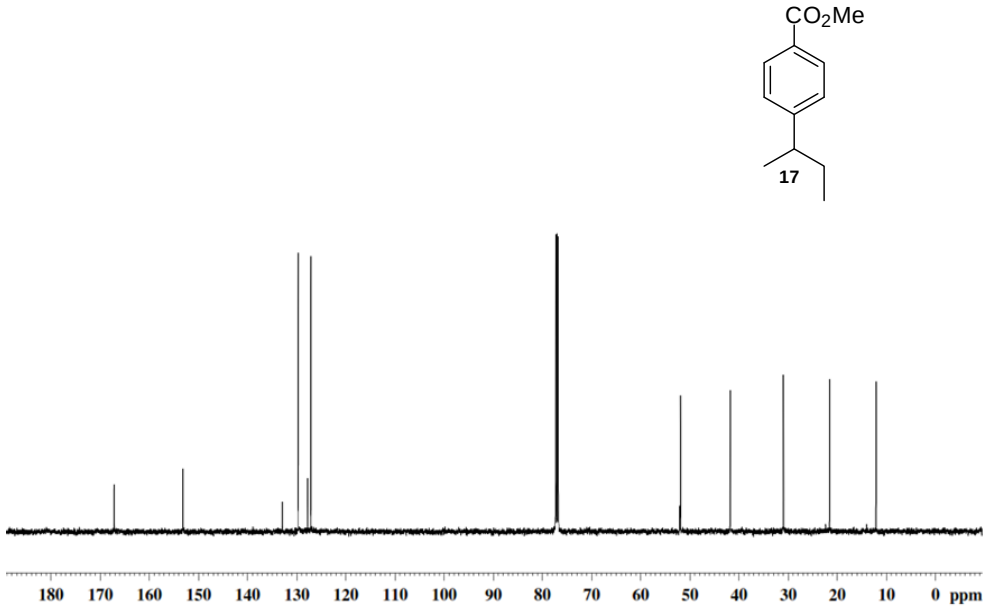
^{1}H NMR($CDCl_3$) of **20**



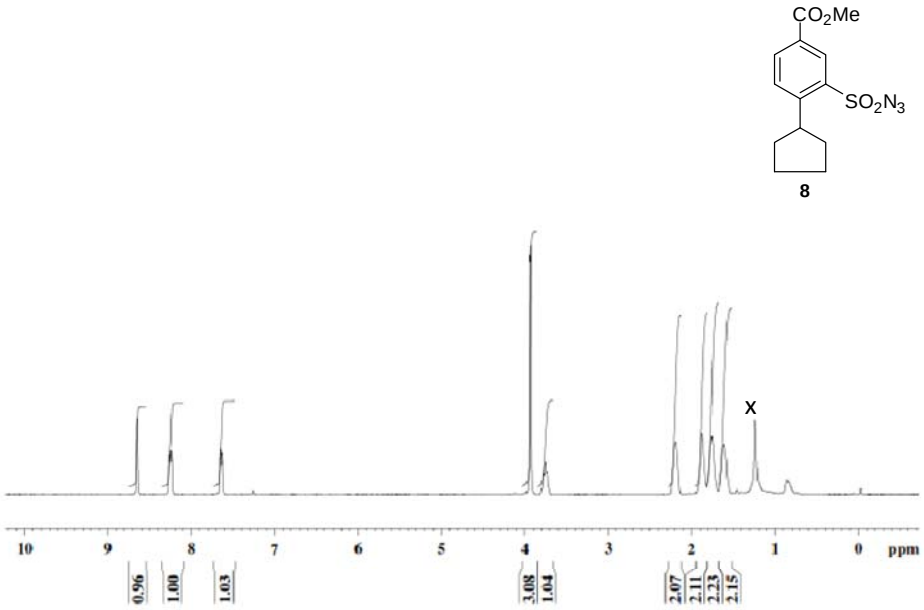
^{13}C NMR($CDCl_3$) of **20**



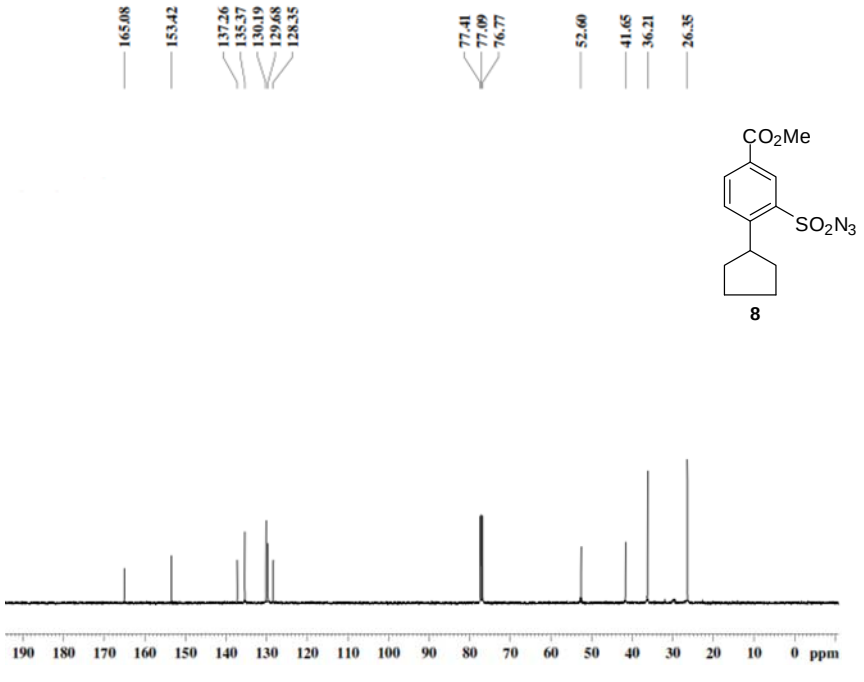
^{1}H NMR($CDCl_3$) of **17**



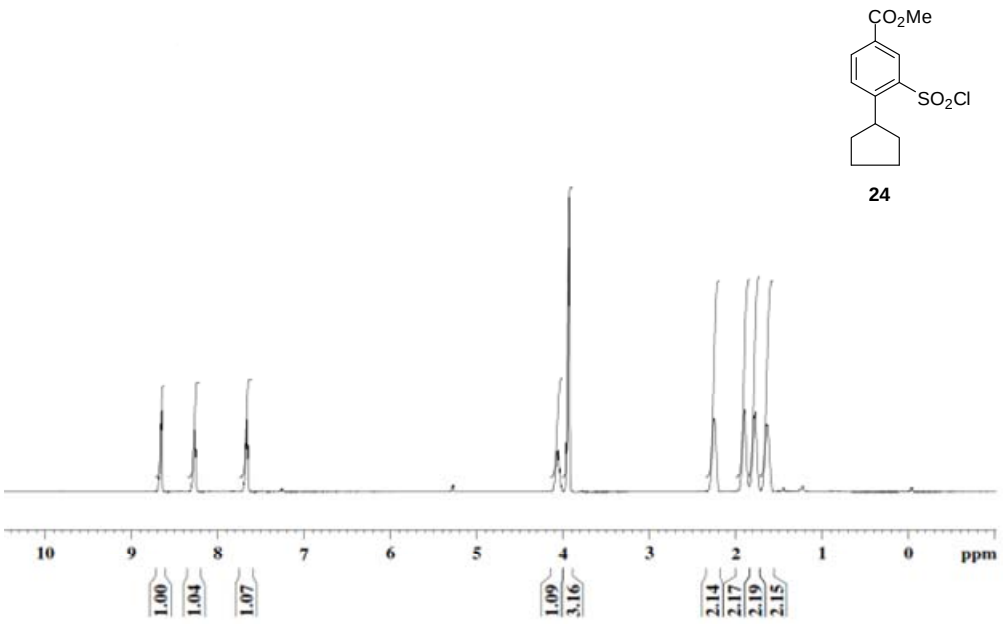
^{13}C NMR($CDCl_3$) of **17**



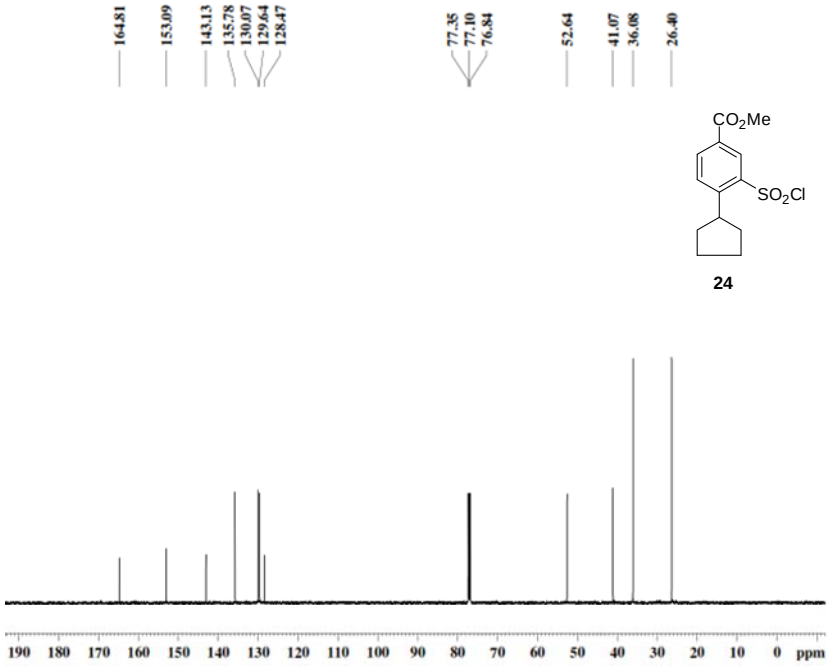
^{1}H NMR($CDCl_3$) of **8**



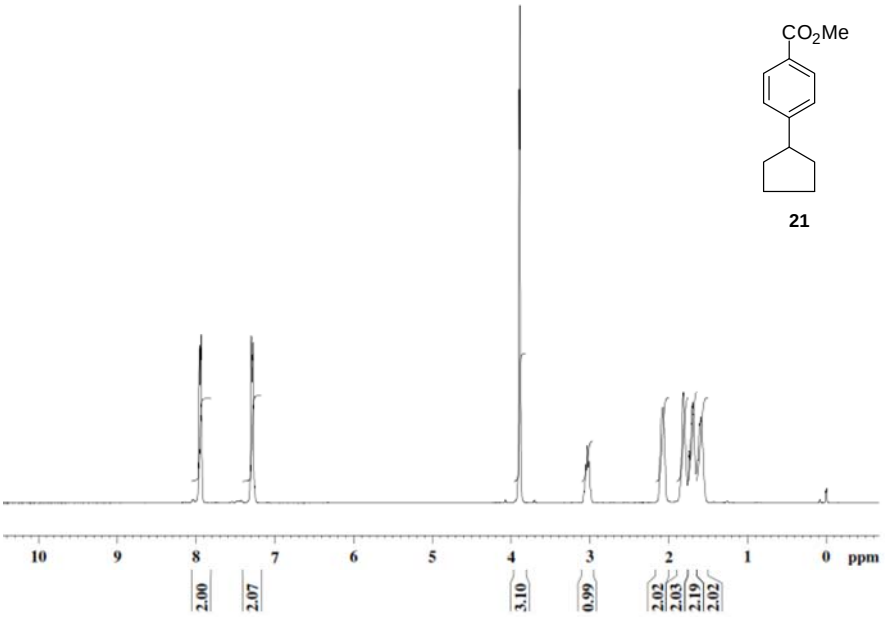
^{13}C NMR($CDCl_3$) of **8**



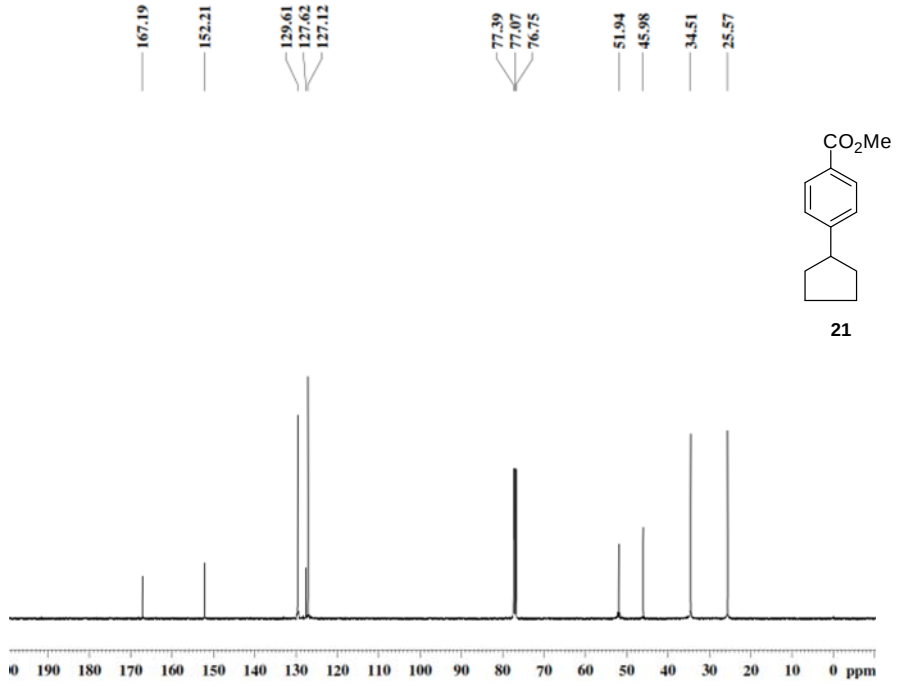
^{1}H NMR($CDCl_3$) of **24**



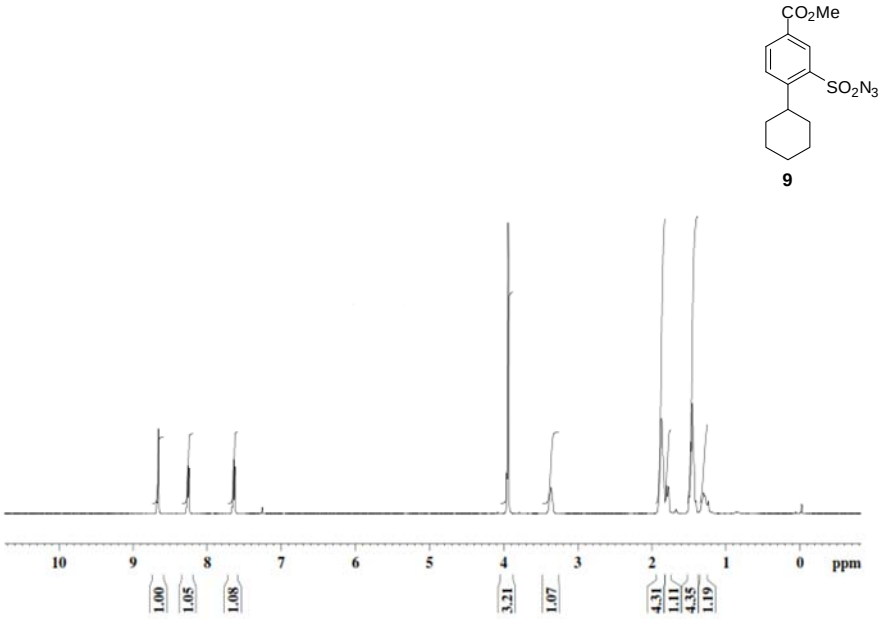
^{13}C NMR($CDCl_3$) of **24**



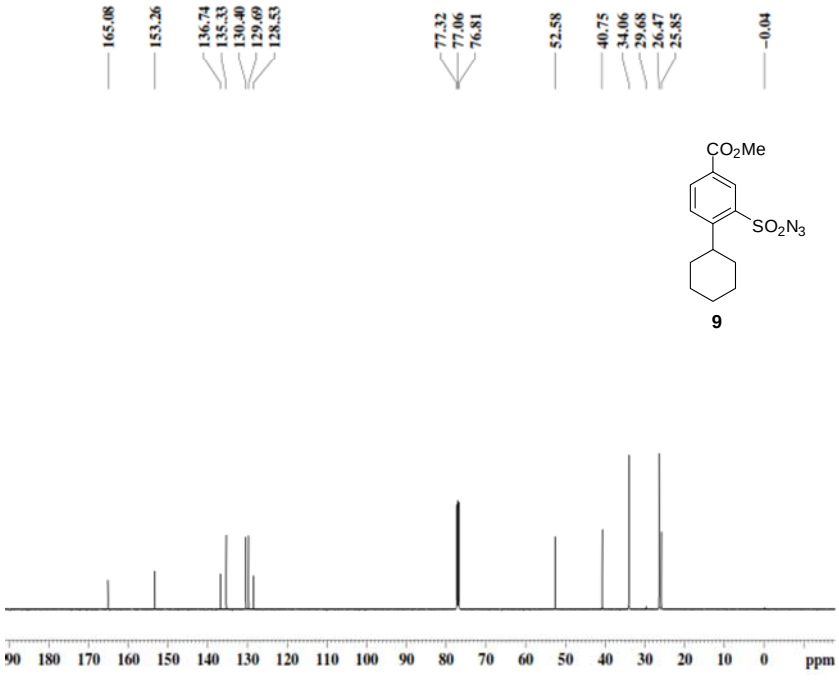
^{1}H NMR($CDCl_3$) of **21**



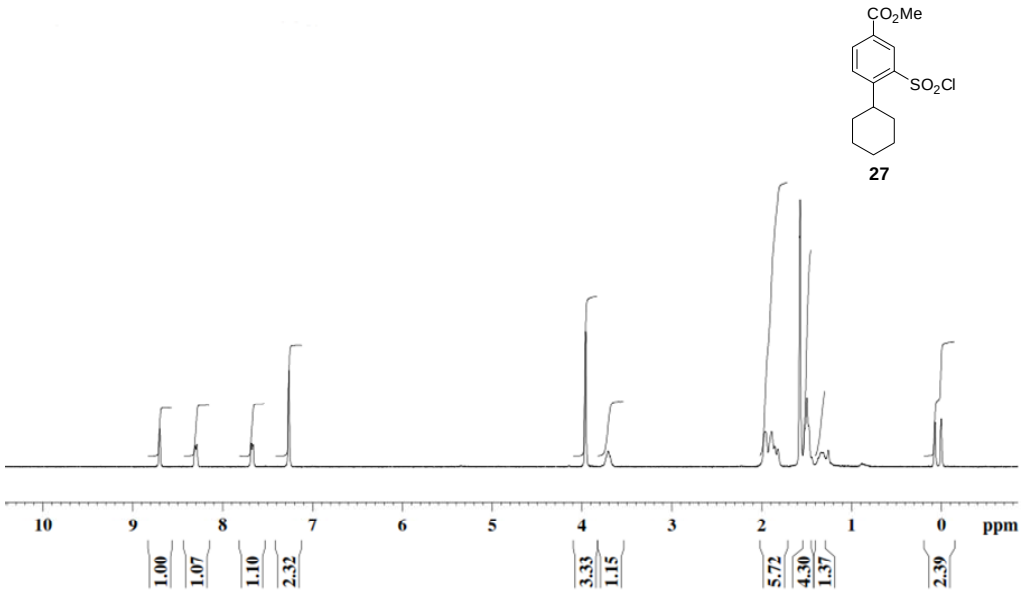
^{13}C NMR($CDCl_3$) of **21**



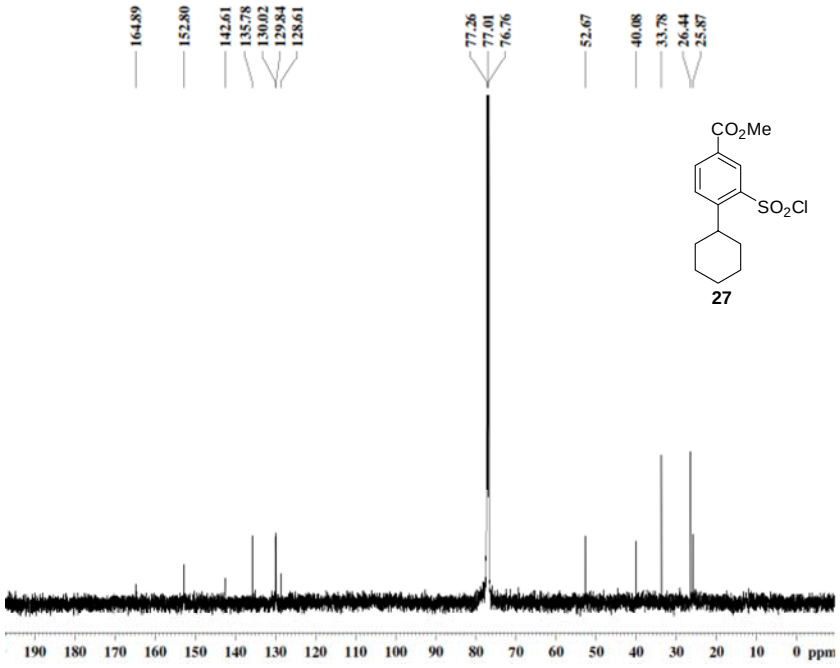
^{1}H NMR($CDCl_3$) of **9**



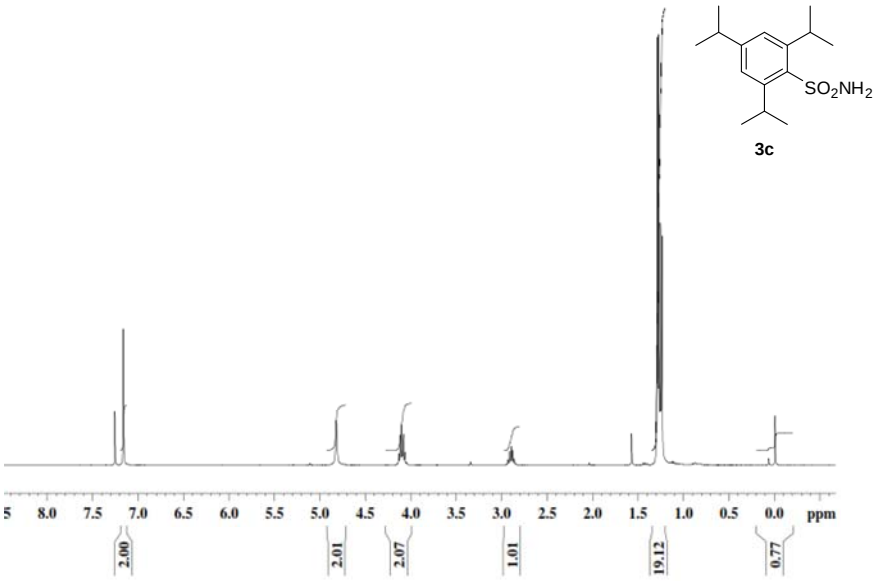
^{13}C NMR($CDCl_3$) of **9**



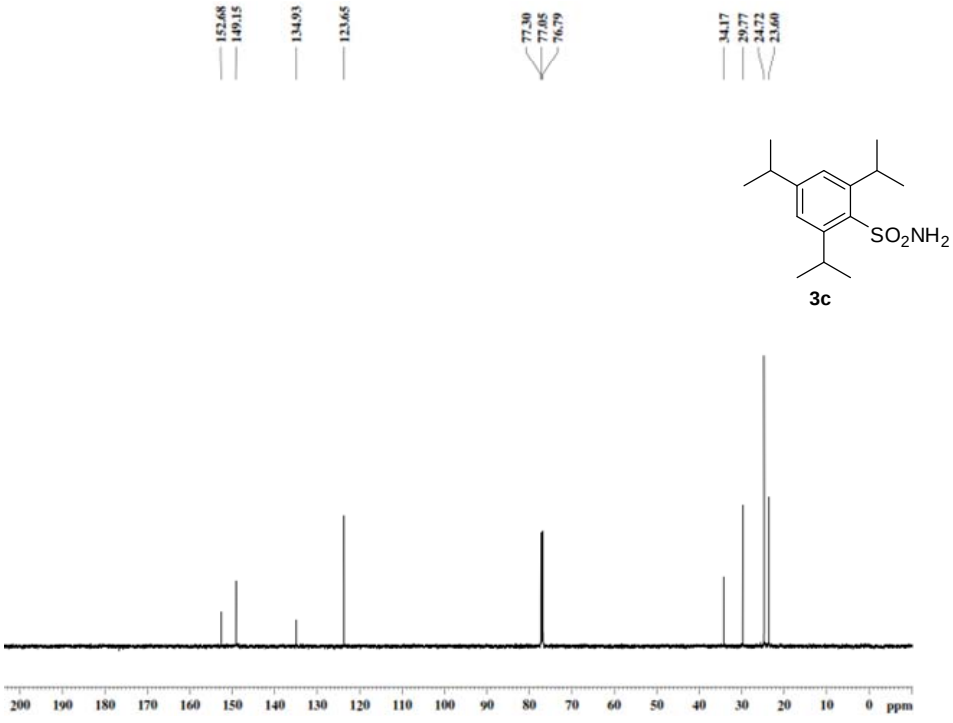
^{1}H NMR($CDCl_3$) of **27**



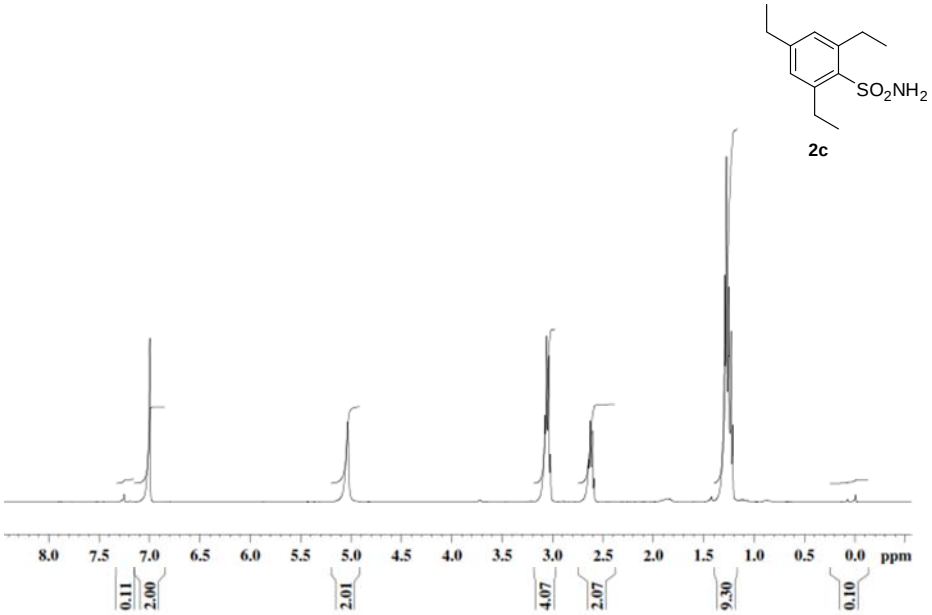
^{13}C NMR($CDCl_3$) of **27**



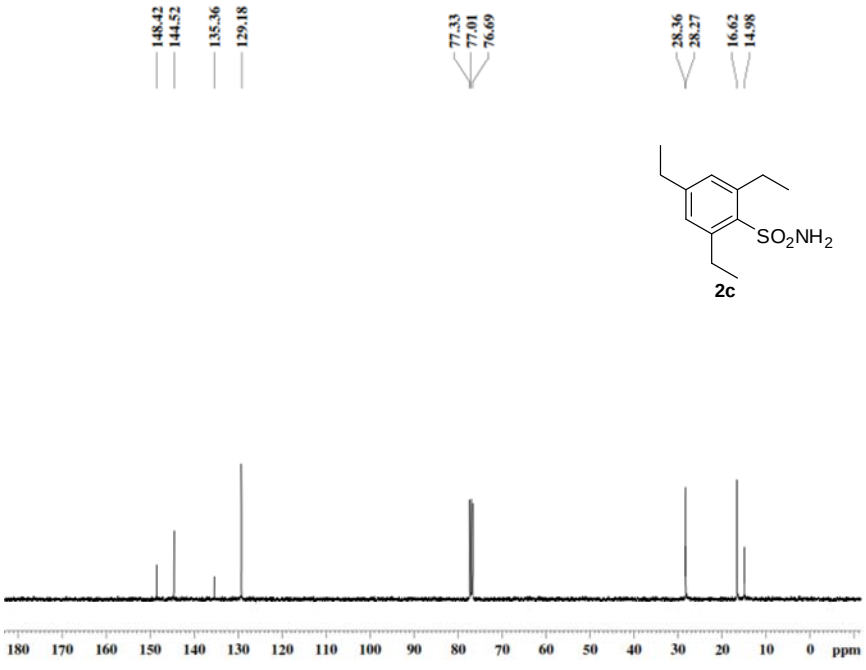
^{1}H NMR($CDCl_3$) of **3c**



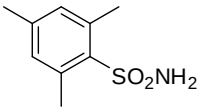
^{13}C NMR($CDCl_3$) of **3c**



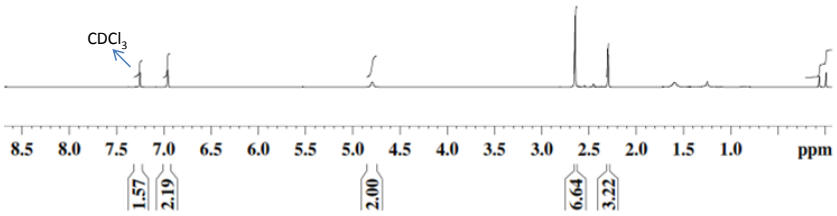
^{1}H NMR($CDCl_3$) of **2c**



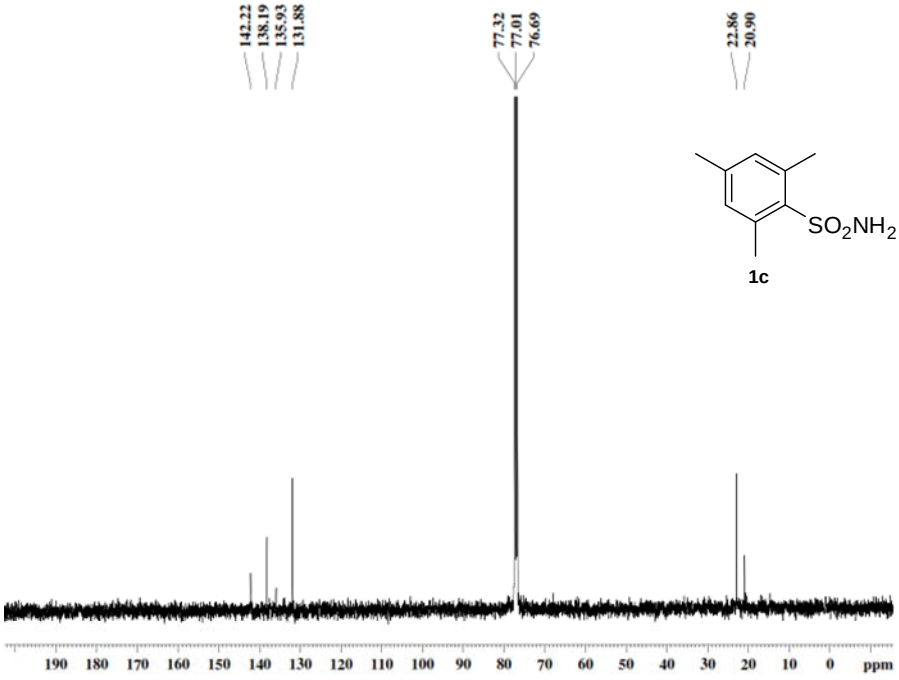
^{13}C NMR($CDCl_3$) of **2c**



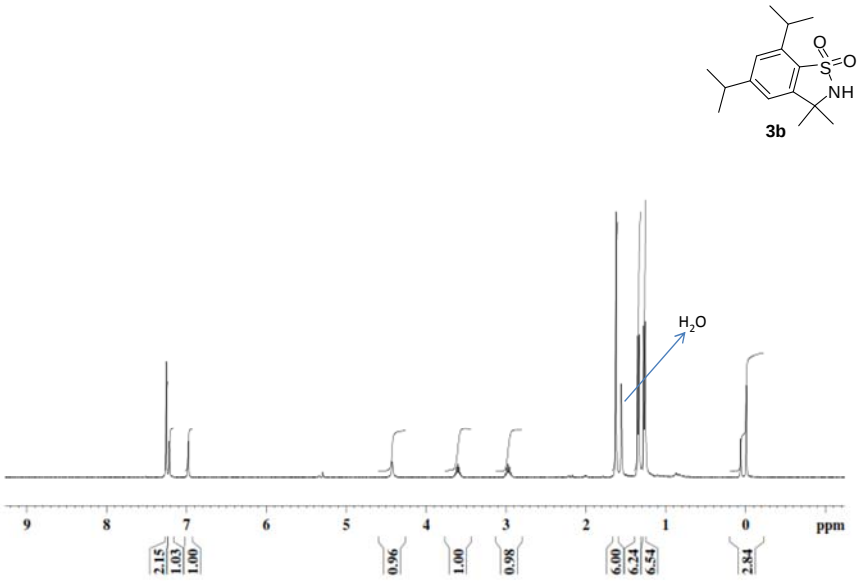
1c



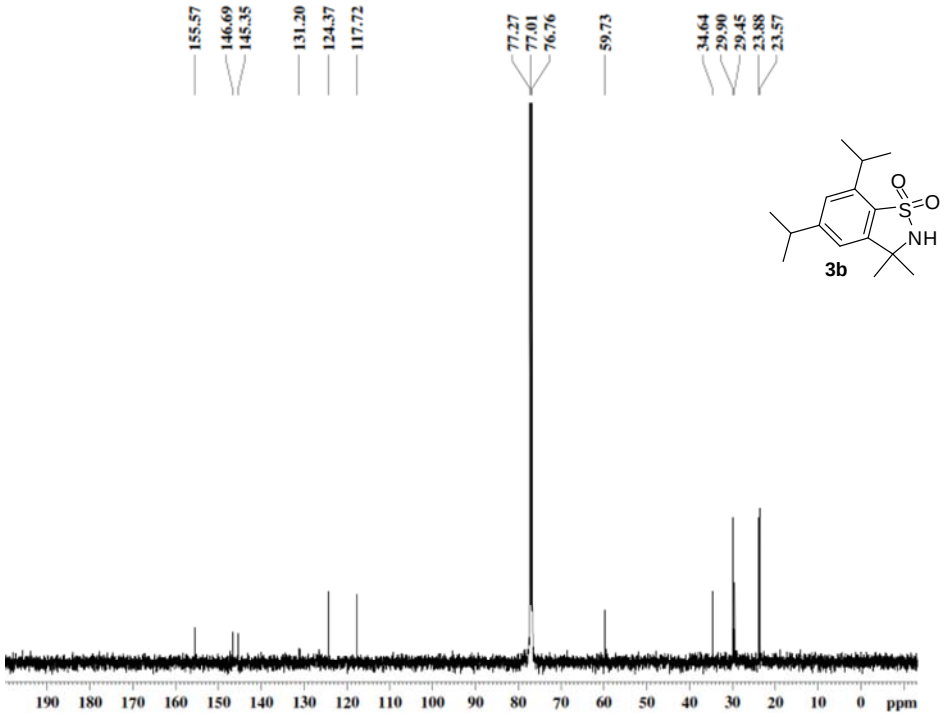
^{1}H NMR($CDCl_3$) of **1c**



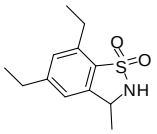
^{13}C NMR($CDCl_3$) of **1c**



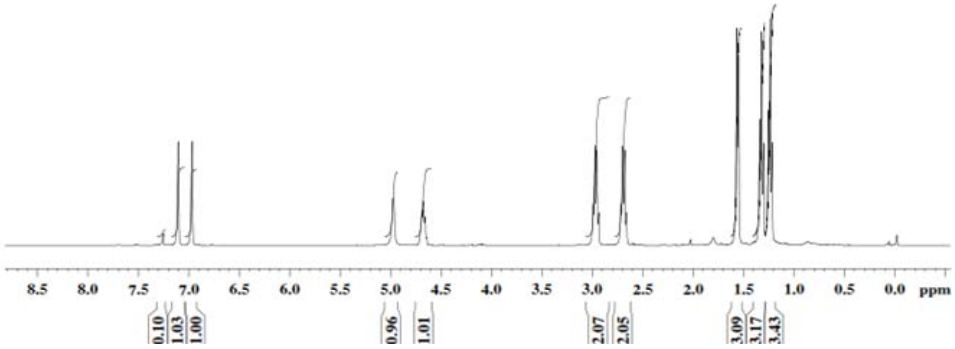
^{1}H NMR($CDCl_3$) of **3b**



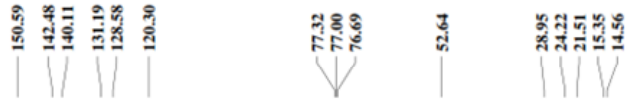
^{13}C NMR($CDCl_3$) of **3b**

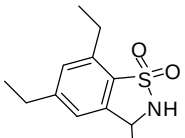


2b

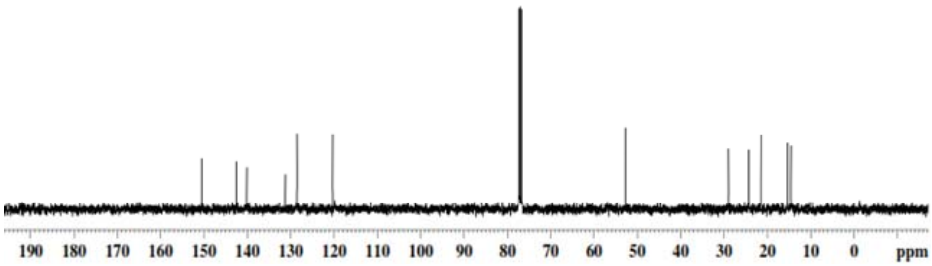


^{1}H NMR($CDCl_3$) of **2b**

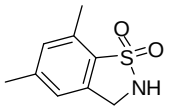




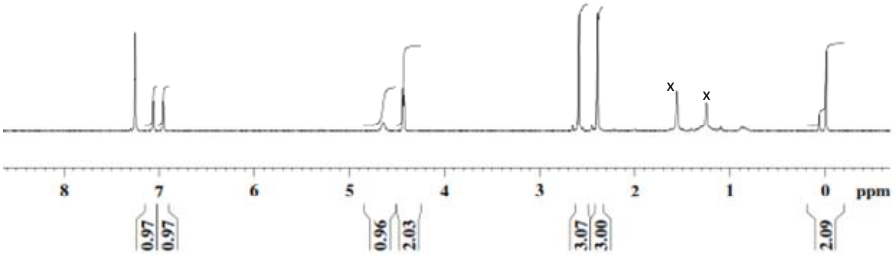
2b



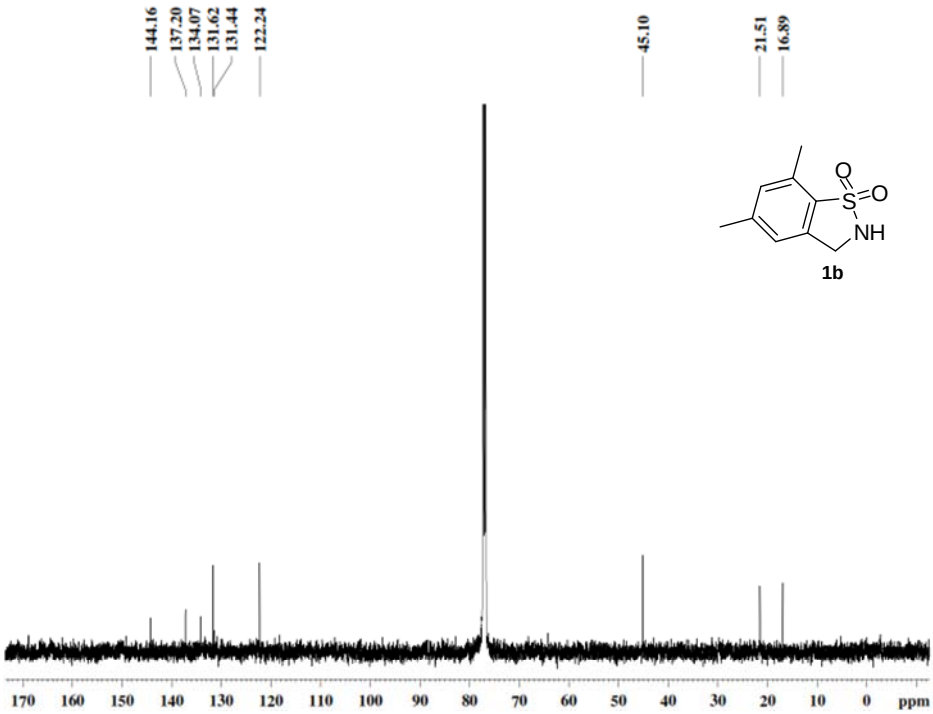
^{13}C NMR($CDCl_3$) of **2b**



1b

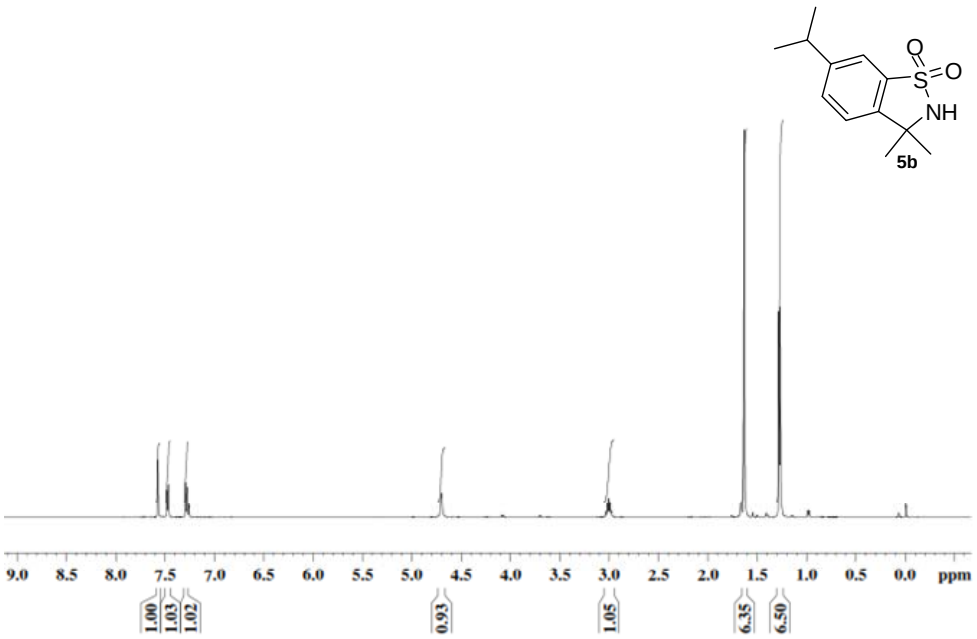


^{1}H NMR($CDCl_3$) of **1b**

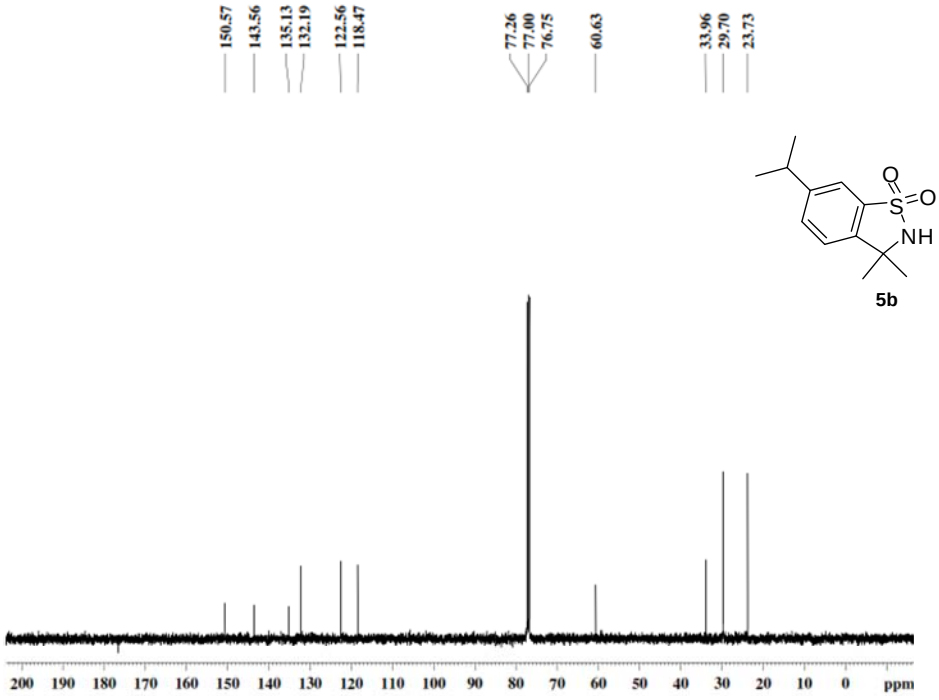


1b

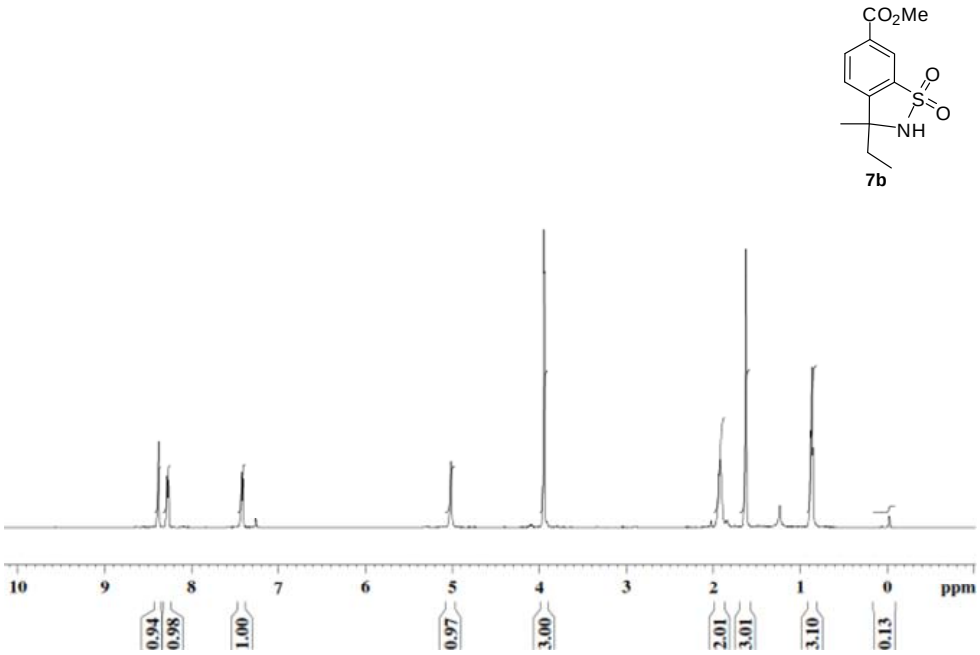
^{13}C NMR($CDCl_3$) of **1b**



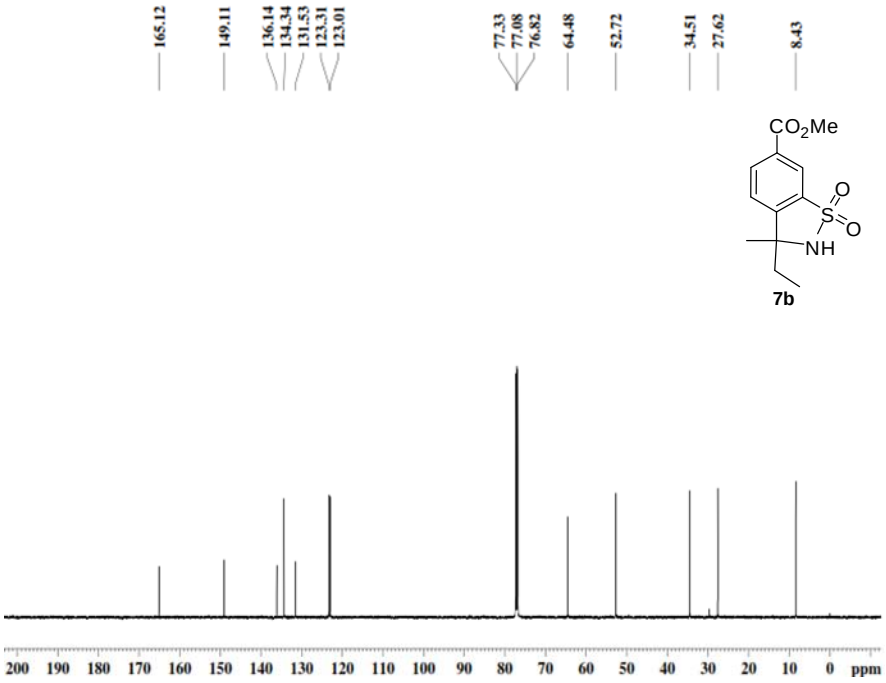
^{1}H NMR($CDCl_3$) of **5b**



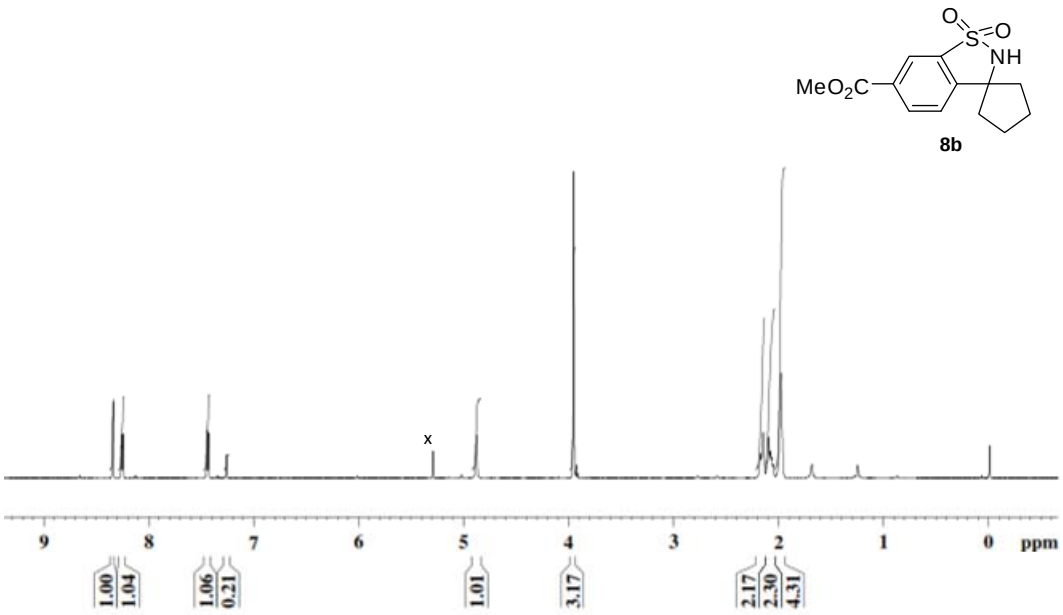
^{13}C NMR($CDCl_3$) of **5b**



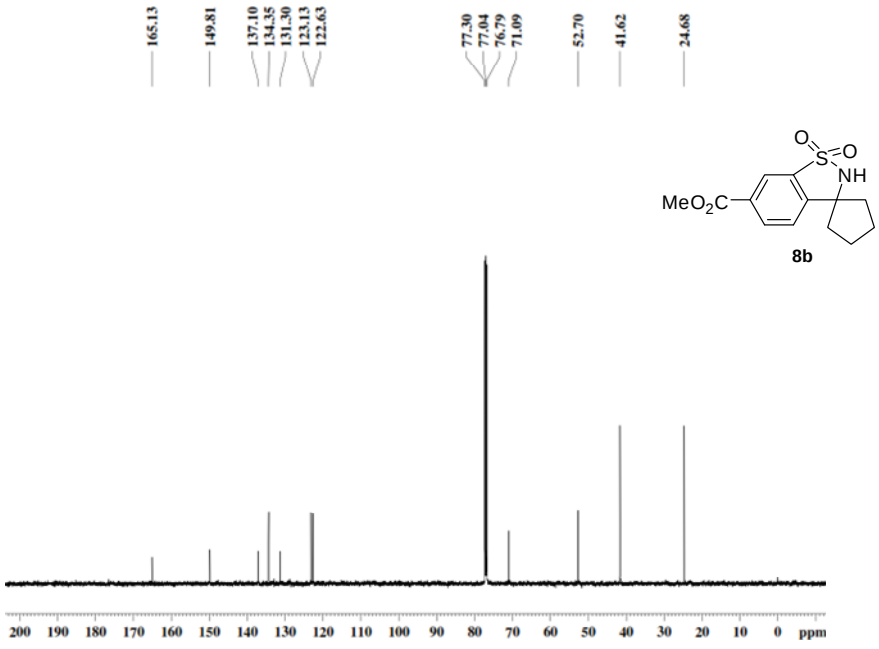
^{1}H NMR($CDCl_3$) of **7b**



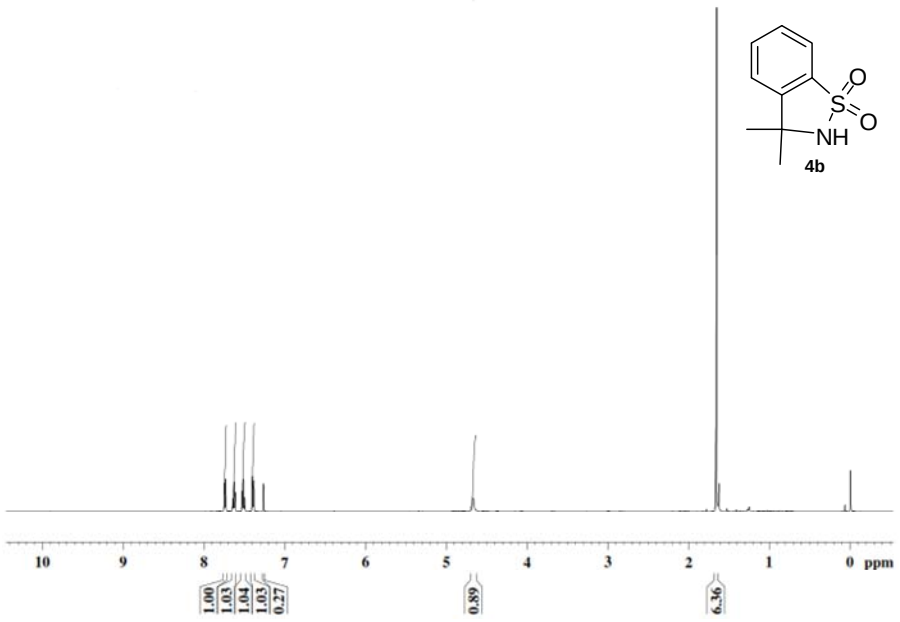
^{13}C NMR($CDCl_3$) of **7b**



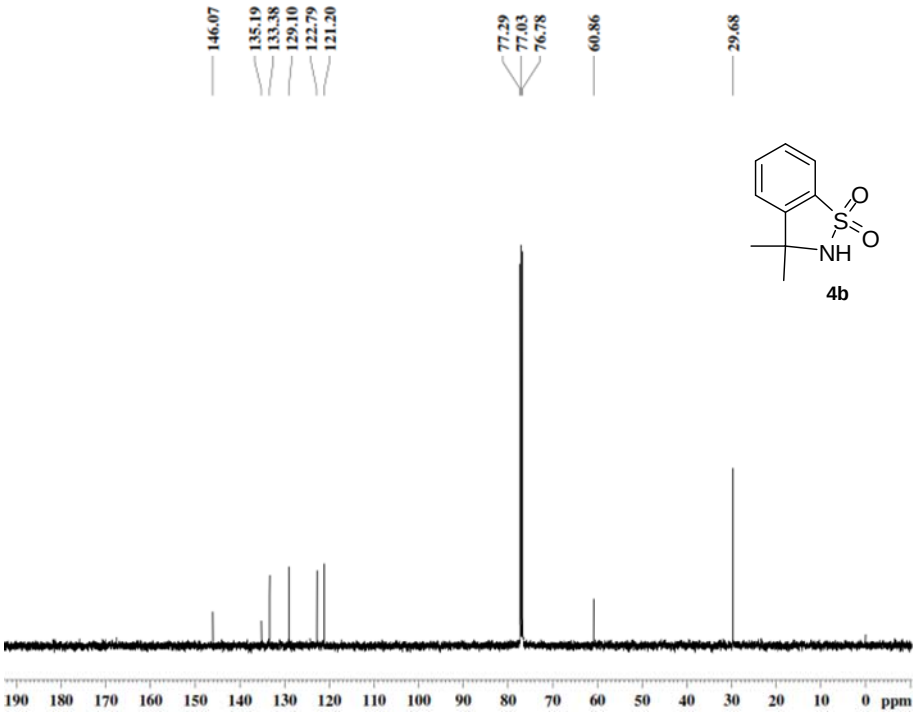
^{1}H NMR($CDCl_3$) of **8b**



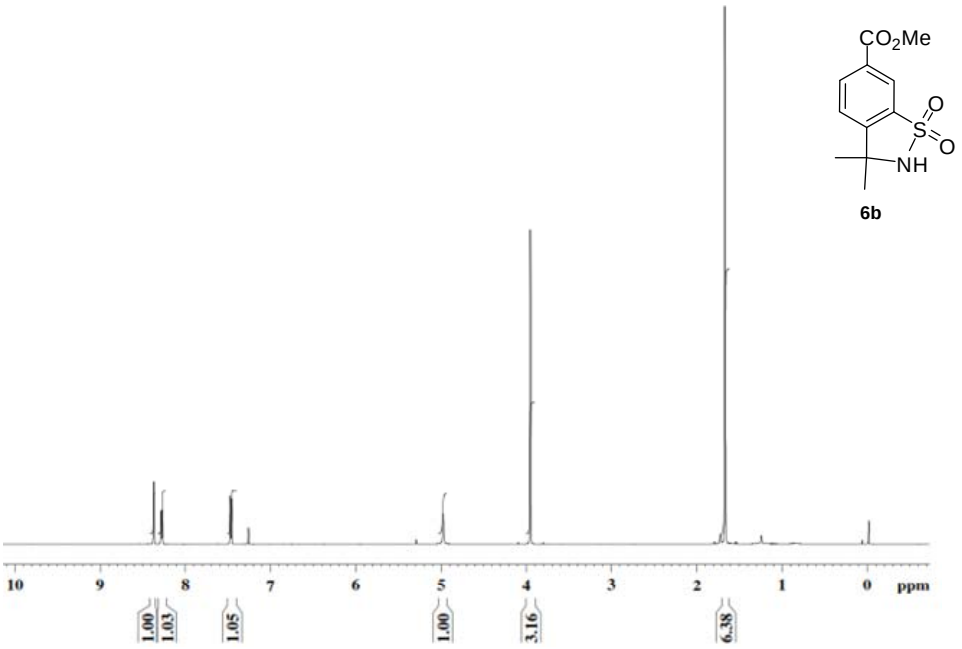
^{13}C NMR($CDCl_3$) of **8b**



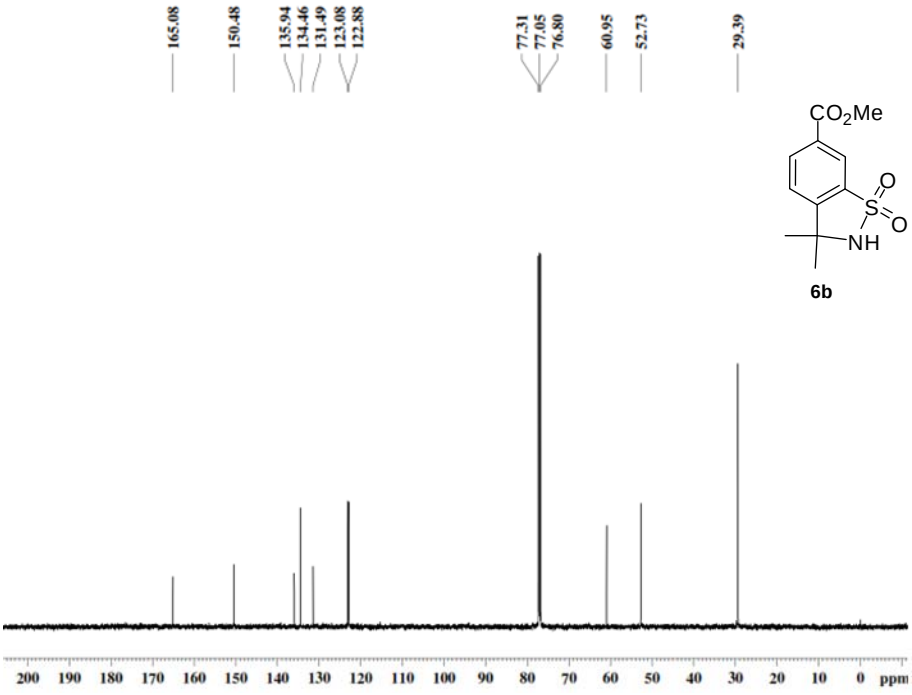
^{1}H NMR($CDCl_3$) of **4b**



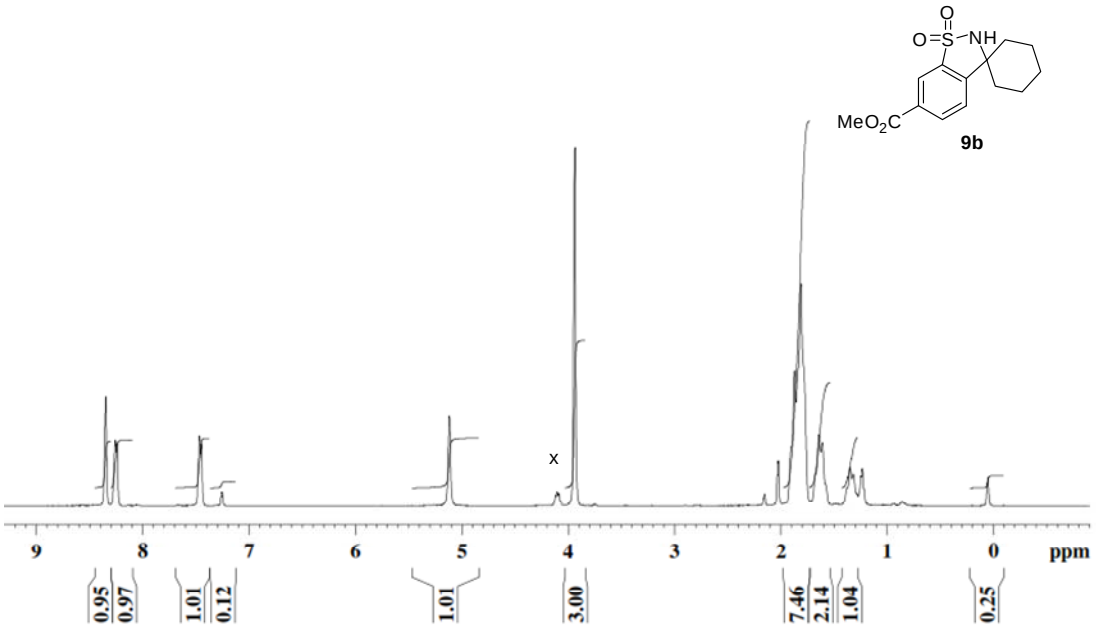
^{13}C NMR($CDCl_3$) of **4b**



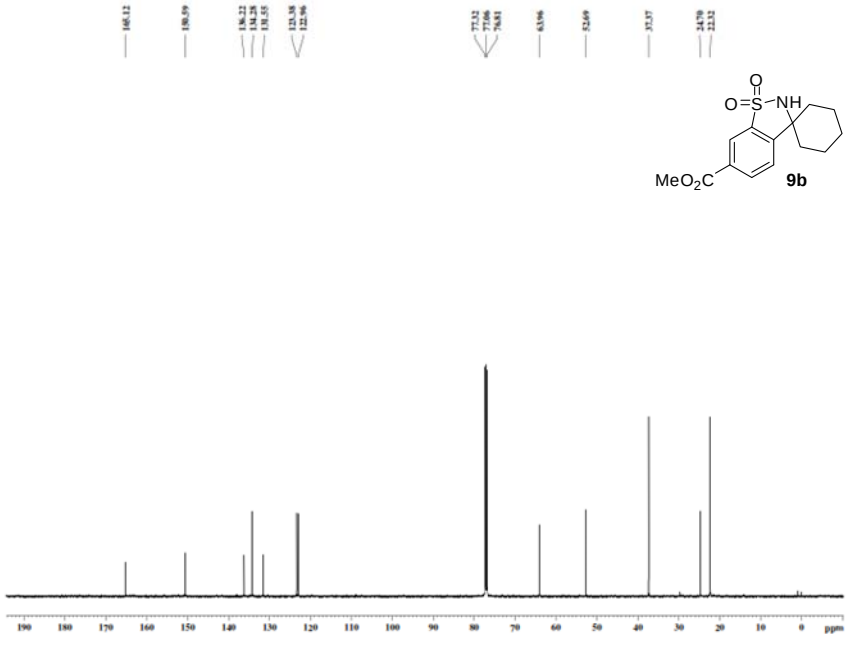
^{1}H NMR($CDCl_3$) of **6b**



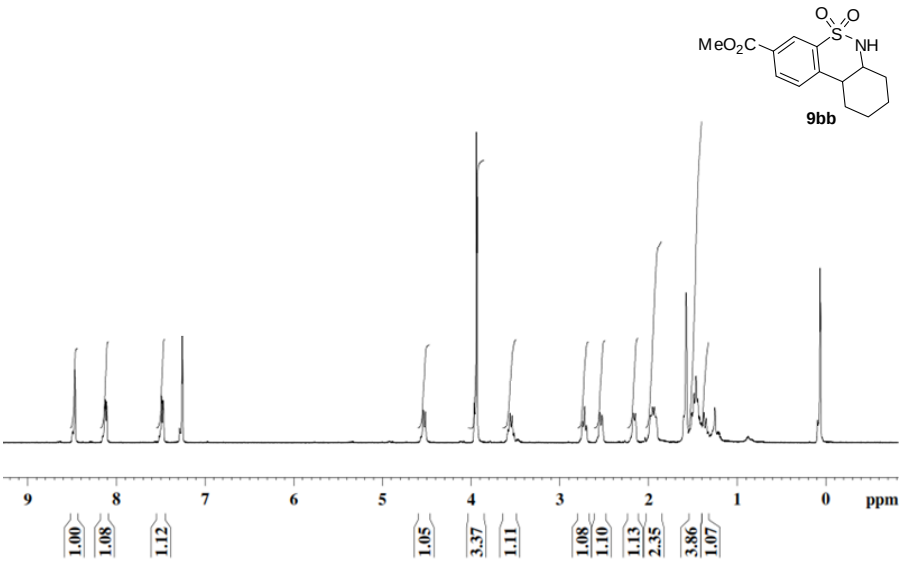
^{13}C NMR($CDCl_3$) of **6b**



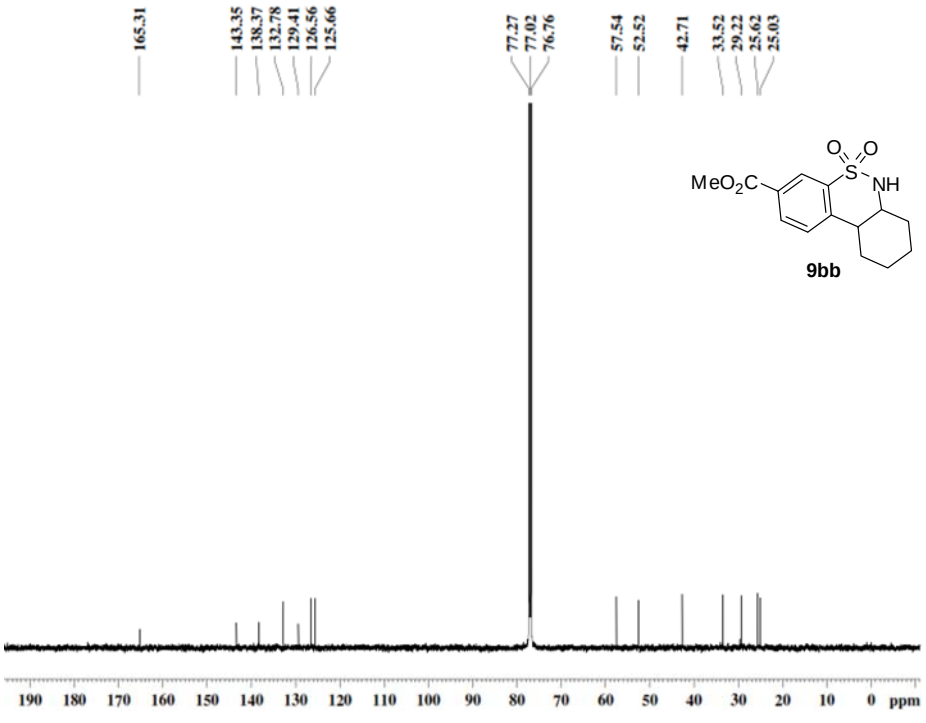
^{1}H NMR($CDCl_3$) of **9b**



^{13}C NMR($CDCl_3$) of **9b**



^{1}H NMR($CDCl_3$) of **9bb**



^{13}C NMR($CDCl_3$) of **9bb**

s

References

(1) (a) Fasan, R.; Meharenna, Y. T.; Snow, C. D.; Poulos, T. L.; Arnold, F. H. *J. Mol. Biol.* **2008**, *383*, 1069; (b) Glieder, A.; Farinas, E. T.; Arnold, F. H. *Nat. Biotechnol.* **2002**, *20*, 1135.

(2) Peters, M. W.; Meinhold, P.; Glieder, A.; Arnold, F. H. *J Am Chem Soc* **2003**, *125*, 13442.

(3) Zhang, K.; El Damaty, S.; Fasan, R. *J Am Chem Soc* **2011**, *133*, 3242.

(4) Ruppel, J. V.; Kamble, R. M.; Zhang, X. P. *Org. Lett.* **2007**, *9*, 4889.

(5) Fey, N.; Howell, J. A. S.; Lovatt, J. D.; Yates, P. C.; Cunningham, D.; McArdle, P.; Gottlieb, H. E.; Coles, S. J. *Dalton Trans.* **2006**, 5464.

(6) Kendall, J.; Jackie, D.; Marshall, A. J. **2009**, *PCT Int. Appl. WO 2009008748 A1*.

(7) Hales, N. J.; Heaney, H.; Hollinshead, J. H.; Ley, S. V. *Tetrahedron* **1995**, *51*, 7741.

(8) Everson, D. A.; Shrestha, R.; Weix, D. J. *J Am Chem Soc* **2010**, *132*, 3636.