Supplementary Data

Indene-based scaffolds. Design and synthesis of novel serotonin 5-HT_6 receptor ligands

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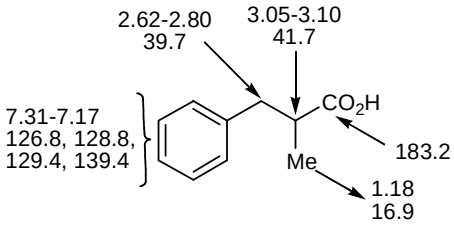
❖ ^{1}H NMR AND ^{13}C NMR ASSIGNMENTS

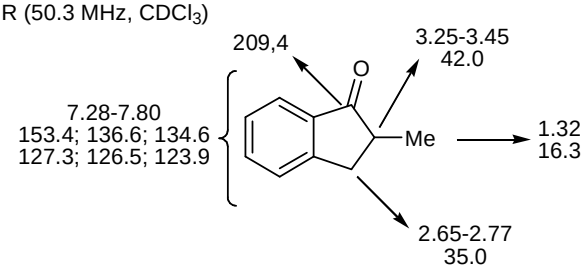
- **2-Methyl-3-phenylpropanoic acid 18**

^{1}H NMR (300 MHz, $CDCl_3$)
^{13}C NMR (75.4 MHz, $CDCl_3$)



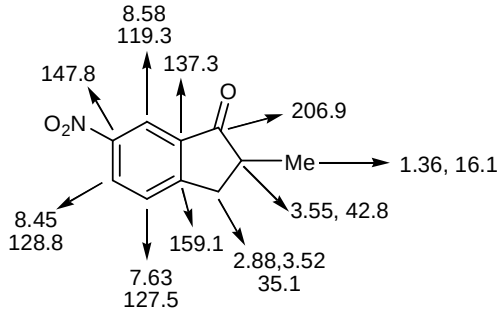
- **2-Methylindan-1-one 19**

^{1}H NMR (200 MHz, $CDCl_3$)
^{13}C NMR (50.3 MHz, $CDCl_3$)



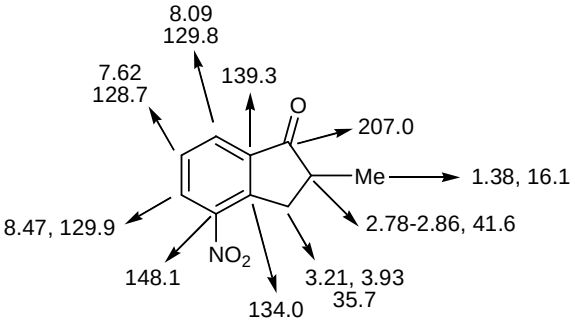
- **2-Methyl-6-nitroindan-1-one 20**

^{1}H NMR ($CDCl_3$, 400 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)
HMQC, HMBC ($CDCl_3$, 400 MHZ)



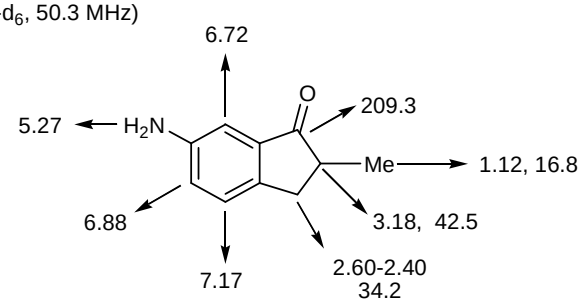
- **2-Methyl-4-nitroindan-1-one 21**

^{1}H NMR ($CDCl_3$, 400 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)
HMQC, HMBC ($CDCl_3$, 400 MHZ)



- **6-Amino-2-methylindan-1-one 22**

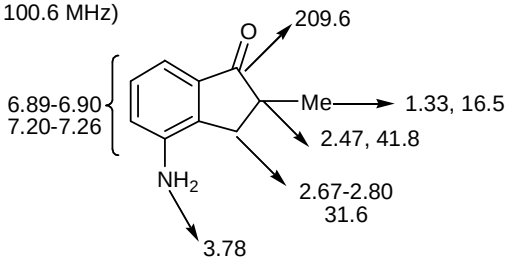
^{1}H NMR (DMSO-d_6, 200 MHz)
^{13}C NMR (DMSO-d_6, 50.3 MHz)



Terniary C: 127.3, 122.9, 106.2
Quaternary C: 148.9, 141.6, 137.2

- **4-Amino-2-methylindan-1-one 23**

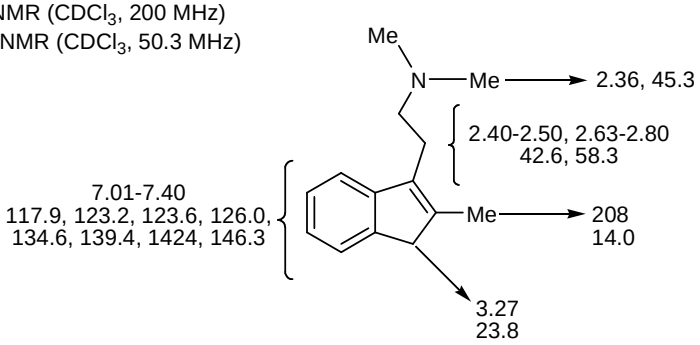
^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C ($CDCl_3$, 100.6 MHz)



Ternary C:113.8, 119.1, 128.7
Quaternary C: 137.1, 138.5, 143.7

- ***N,N*-Dimethyl-2-(2-methyl-1*H*-inden-3-yl)ethanamine 25**

^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



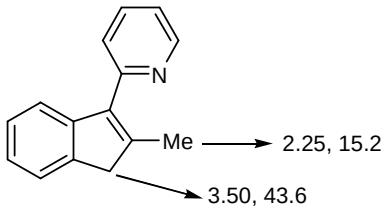
- **2-(2-Methyl-1*H*-inden-3-yl)pyridine 26**

^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)

8.76, 7.78, 7.46-7.42, 7.28-7.10

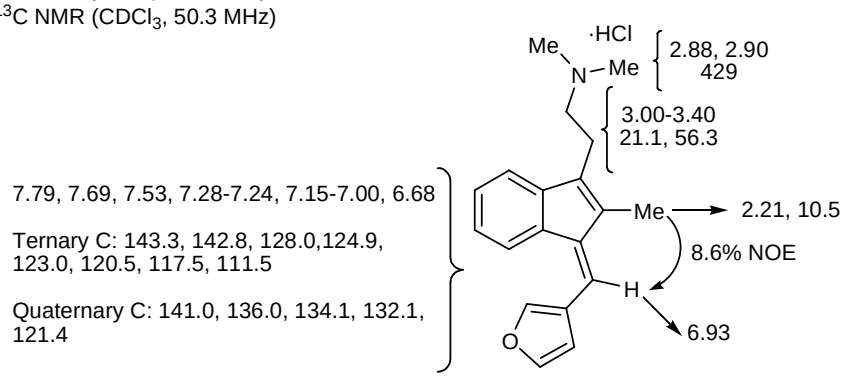
Ternary C: 1496, 136.1, 126.1,
124.1, 123.2, 121.6, 119.7

Quaternary C: 145.2, 143.8, 142.1



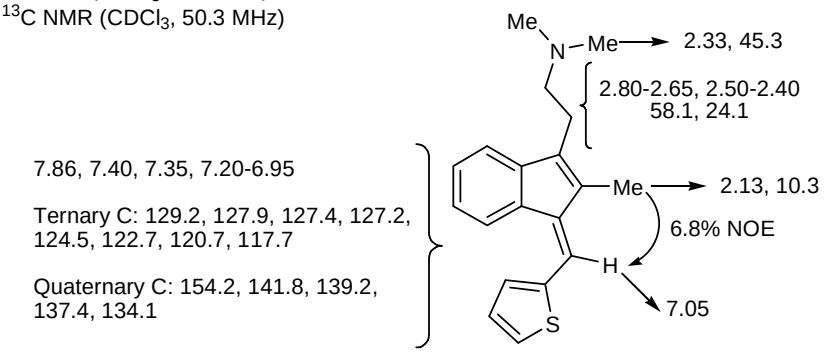
- **2-[(1*Z*)-1-(3-Furylmethylidene)-2-methyl-1*H*-inden-3-yl]-*N*,*N*-dimethylethanamine hydrochloride 8**

^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



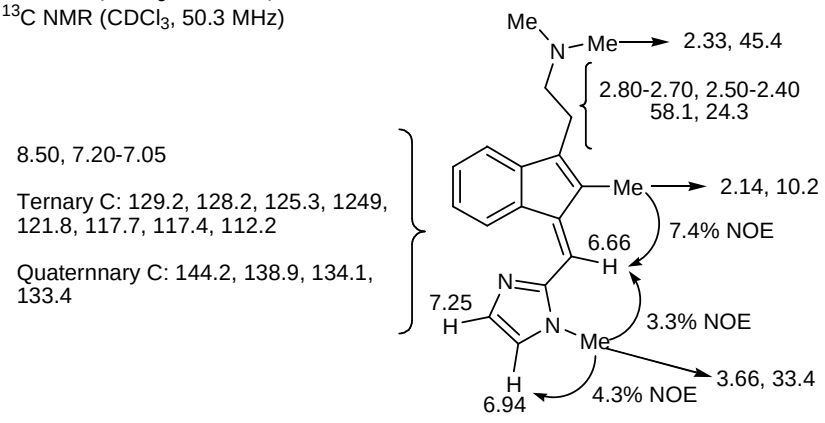
- ***N*,*N*-Dimethyl-2-[(1*Z*)-2-methyl-1-(2-thienylmethylidene)-1*H*-inden-3-yl]ethanamine 9**

^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



- ***N*,*N*-Dimethyl-2-{(1*Z*)-2-methyl-1-[(1-methyl-1*H*-imidazol-2-yl)methylidene]-1*H*-inden-3-yl}ethanamine 10**

^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



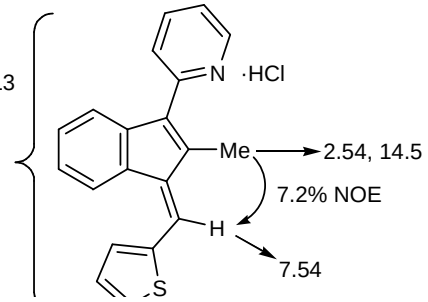
- **2-[(1*Z*)-2-Methyl-1-(2-thienylmethylidene)-1*H*-inden-3-yl]pyridine hydrochloride 11·HCl**

^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)

9.05, 8.46, 8.23, 8.01, 7.86, 7.60-7.55, 7.22-7.13

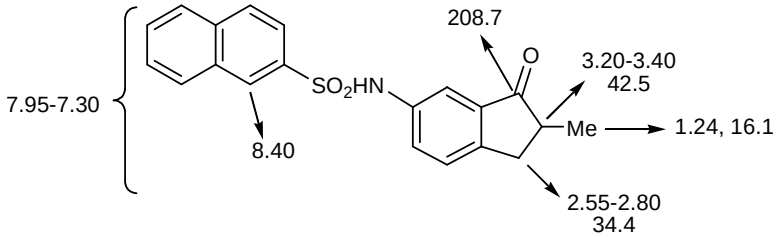
Ternary C: 133.5, 131.8, 129.6, 128.7, 128.0, 125.9, 123.3, 120.0

Quaternary C: 149.9, 147.3, 144.9, 143.6, 141.1, 139.6, 138.2



- ***N*-(2-Methyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl)naphthalene-2-sulfonamide 28**

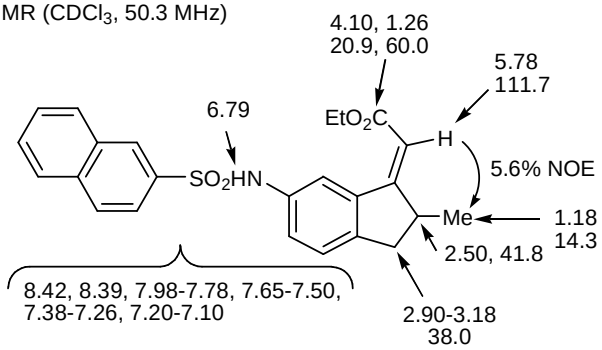
^{1}H, ^{13}C NMR ($CDCl_3$, 200 MHz)



Ternary C: 129.5, 129.2, 128.9, 128.3, 127.8, 127.5, 127.4, 122.9, 116.0
Quaternary C: 150.2, 137.2, 136.2, 135.6, 134.9, 131.9

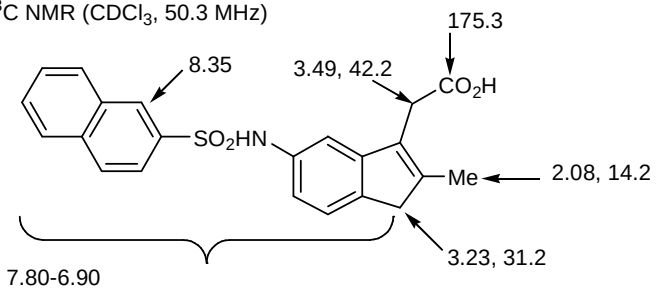
- **Ethyl (2*Z*)-{2-methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetate 32**

^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



- **{2-Methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetic acid 33**

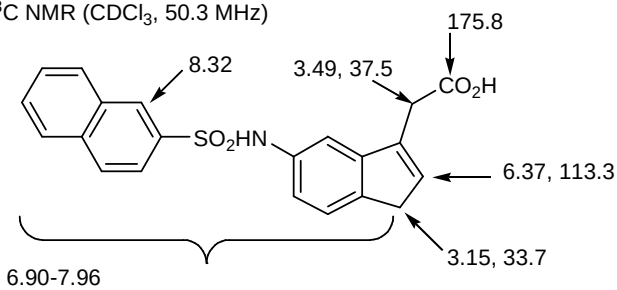
^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



7.80-6.90
Terniary C: 129.2, 128.8, 128.6, 127.7, 127.2, 123.5, 122.2, 117.3, 112.4
Quaternary C: 146.7, 144.2, 139.0, 135.8, 134.9, 134.7, 131.8

- **{5-[(2-Naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetic acid 36**

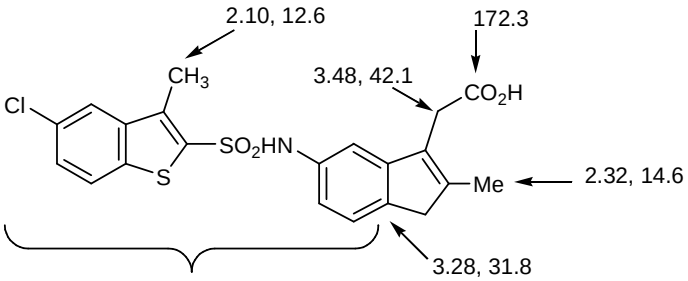
^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



6.90-7.96
Terniary C: 118.6, 122.2, 124.1, 127.2, 127.6, 128.6, 129.1, 129.2, 133.8
Quaternary C: 131.8, 134.7, 134.9, 135.7, 141.0, 145.3,

- **(5-{[(5-Chloro-3-methylbenzo[*b*]thien-2-yl)sulfonyl]amino}-2-methyl-1*H*-inden-3-yl)acetic acid 37**

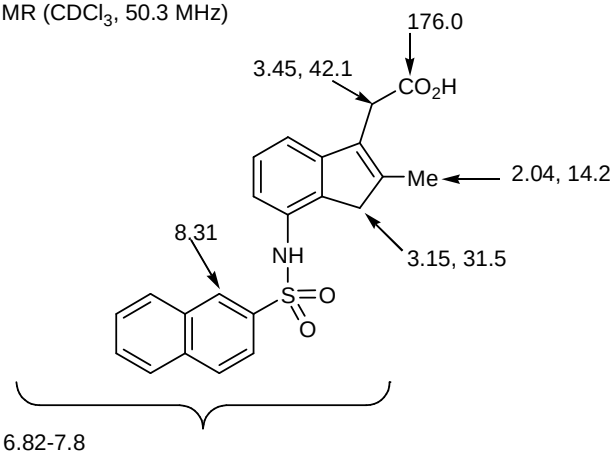
^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



6.86-7.61
Terniary C: 112.2, 117.2, 124.0, 125.2, 128.0
Quaternary C: 130.2. 131.2, 135.8, 137.2, 138.1, 139.0, 140.8, 144.0, 147.8

- **{2-Methyl-7-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetic acid 38**

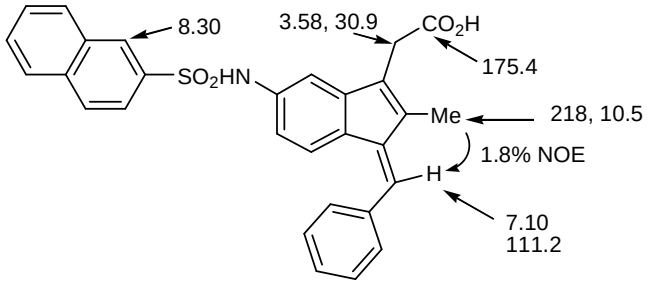
^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



6.82-7.8
Terniary C: 112.4, 117.5, 122.2, 123.5, 127.2, 127.6, 128.5, 128.8, 129.1, 129.2
Quaternary C: 131.8, 134.6, 134.9135.8, 139./, 144.2, 147.4

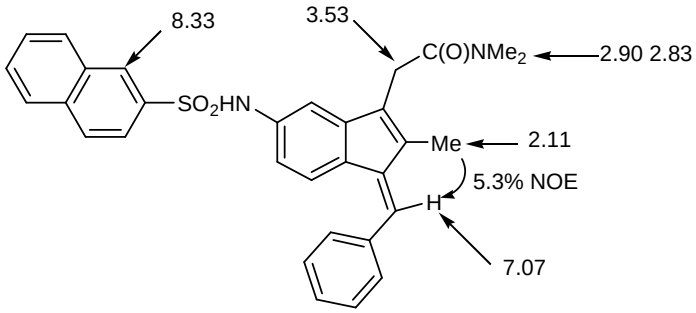
- **{(1*Z*)-1-Benzylidene-2-methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetic acid 39**

^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



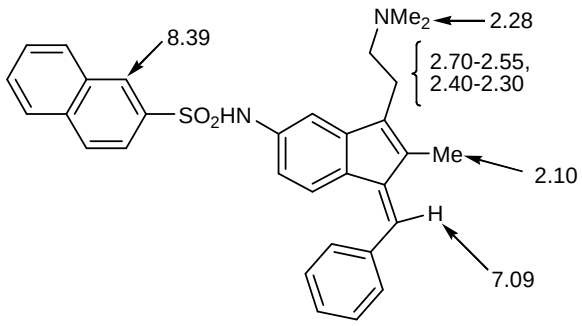
- ***N*,*N*-Dimethyl-2-{(1*Z*)-1-benzylidene-2-methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetamide 40**

^{1}H NMR ($CDCl_3$, 200 MHz)



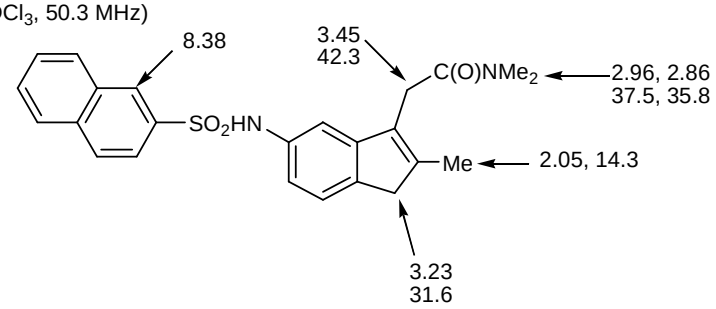
- ***N*-{(1*Z*)-1-Benzylidene-3-[2-(dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 12**

^{1}H NMR ($CDCl_3$, 200 MHz)



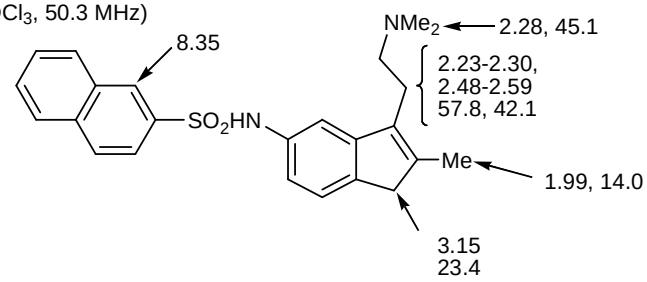
- ***N*,*N*-Dimethyl-2-{2-methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetamide 41**

^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



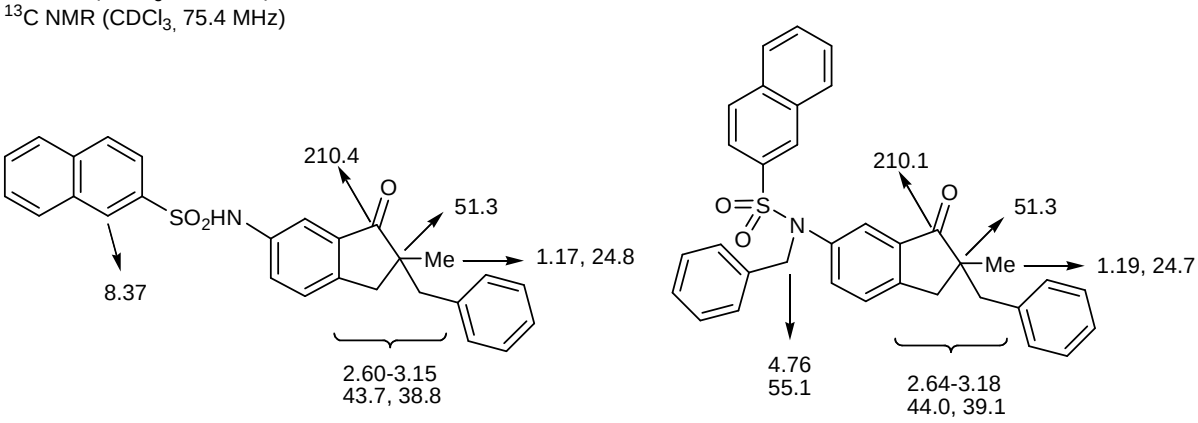
- ***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 13**

^{1}H NMR ($CDCl_3$, 200 MHz)
^{13}C NMR ($CDCl_3$, 50.3 MHz)



- ***N*-(2-benzyl-2-methyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl)naphthalene-2-sulfonamide 49 and *N*-benzyl-*N*-(2-methyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl)naphthalene-2-sulfonamide 50**

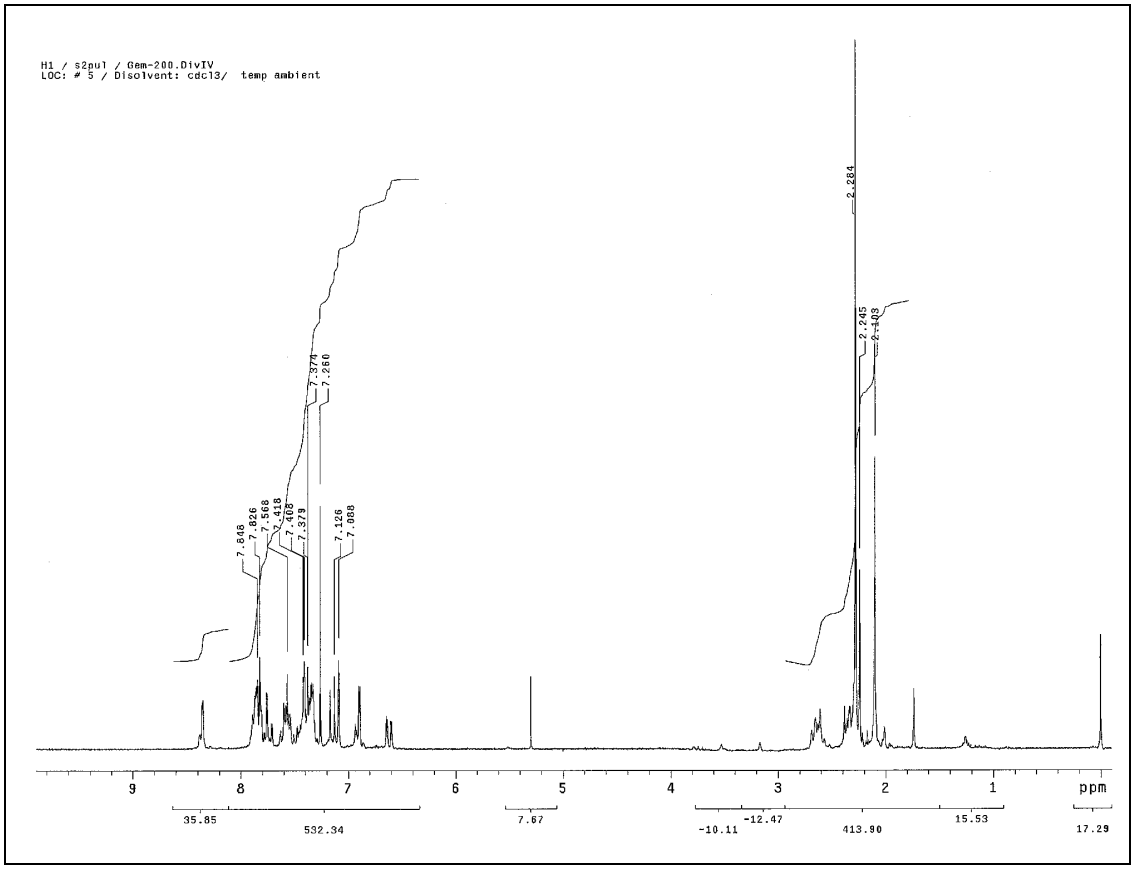
^{1}H NMR ($CDCl_3$, 300 MHz)
^{13}C NMR ($CDCl_3$, 75.4 MHz)



❖ NMR SPECTRA OF TARGETED COMPOUNDS

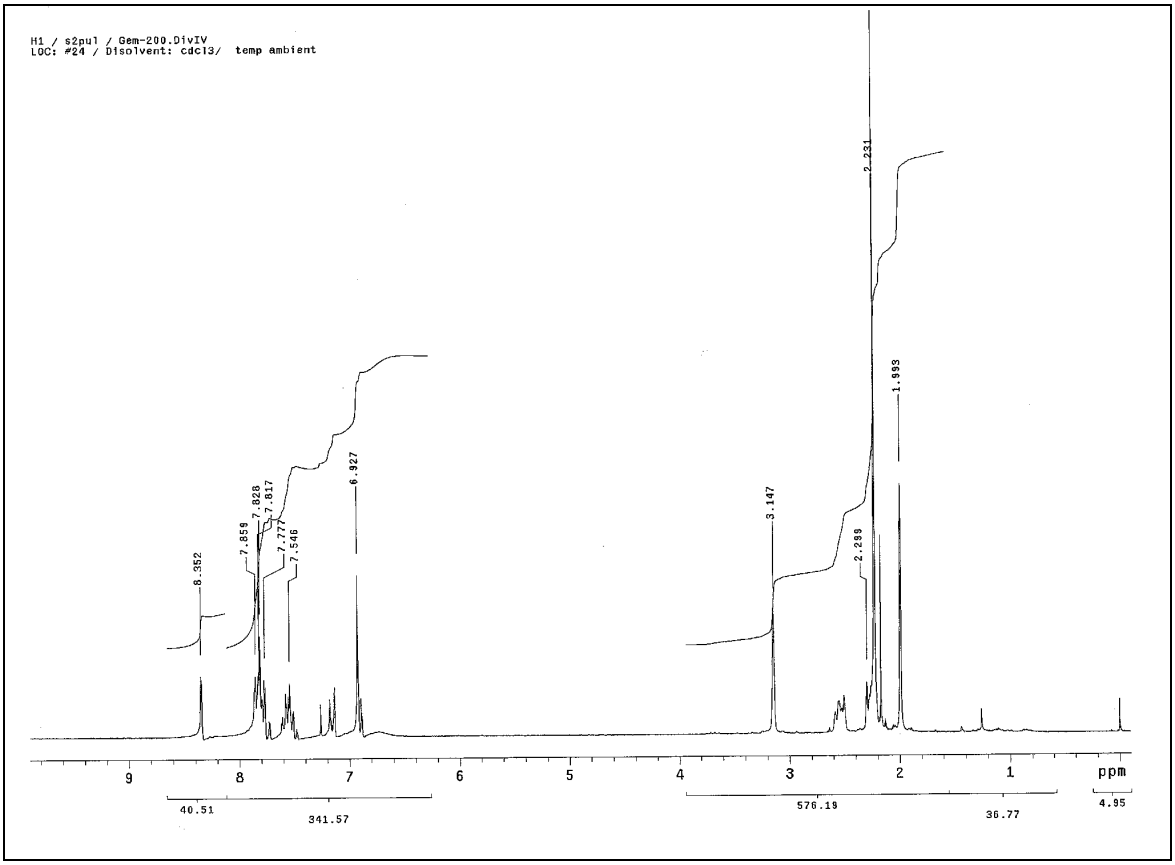
- ***N*-{(1*Z*)-1-Benzylidene-3-[2-(dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 12**

^{1}H NMR (200 MHz, $CDCl_3$)

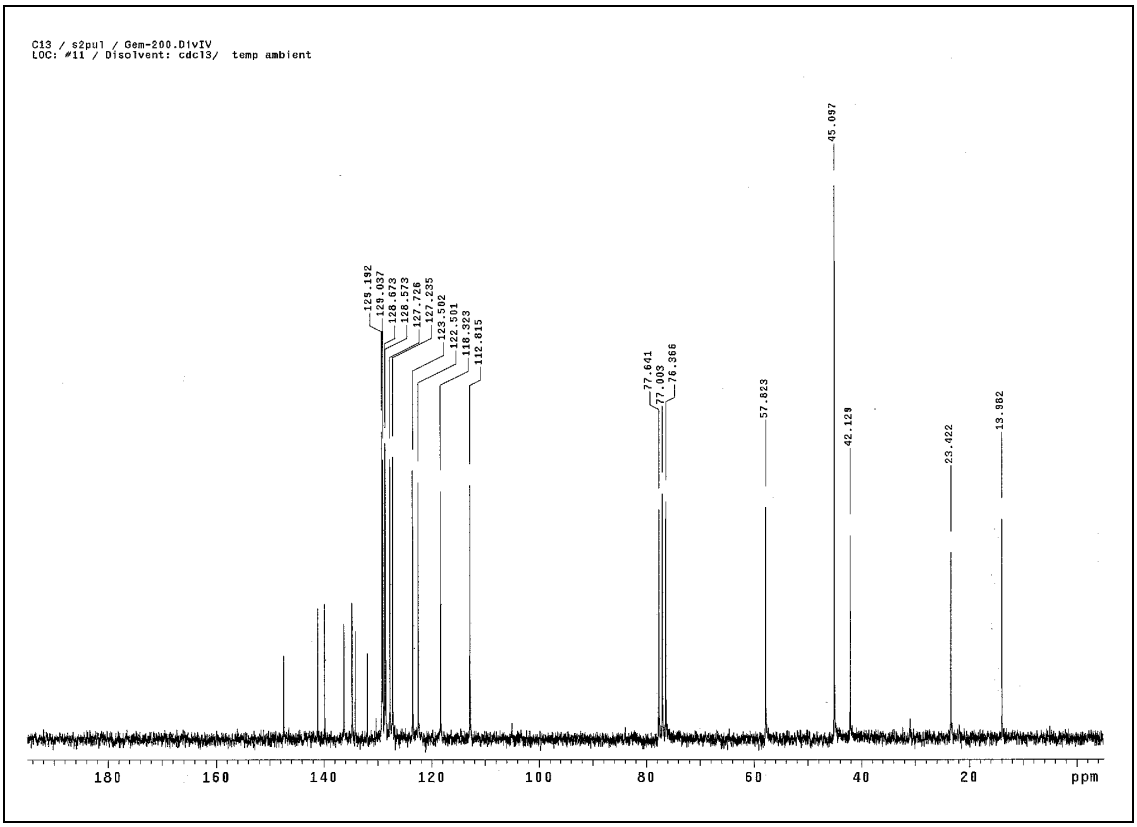


- ***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 13**

^{1}H NMR (200 MHz, $CDCl_3$)

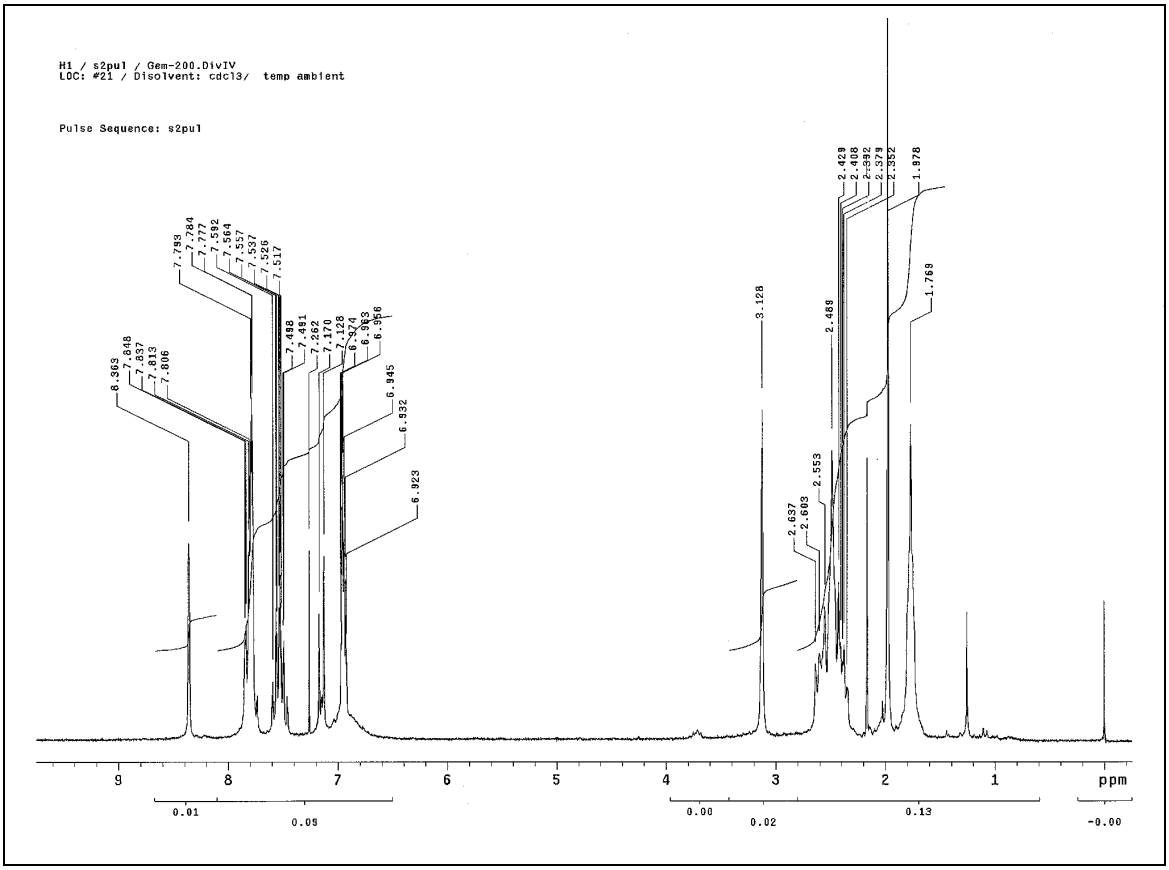


^{13}C NMR (50.3 MHz, $CDCl_3$)

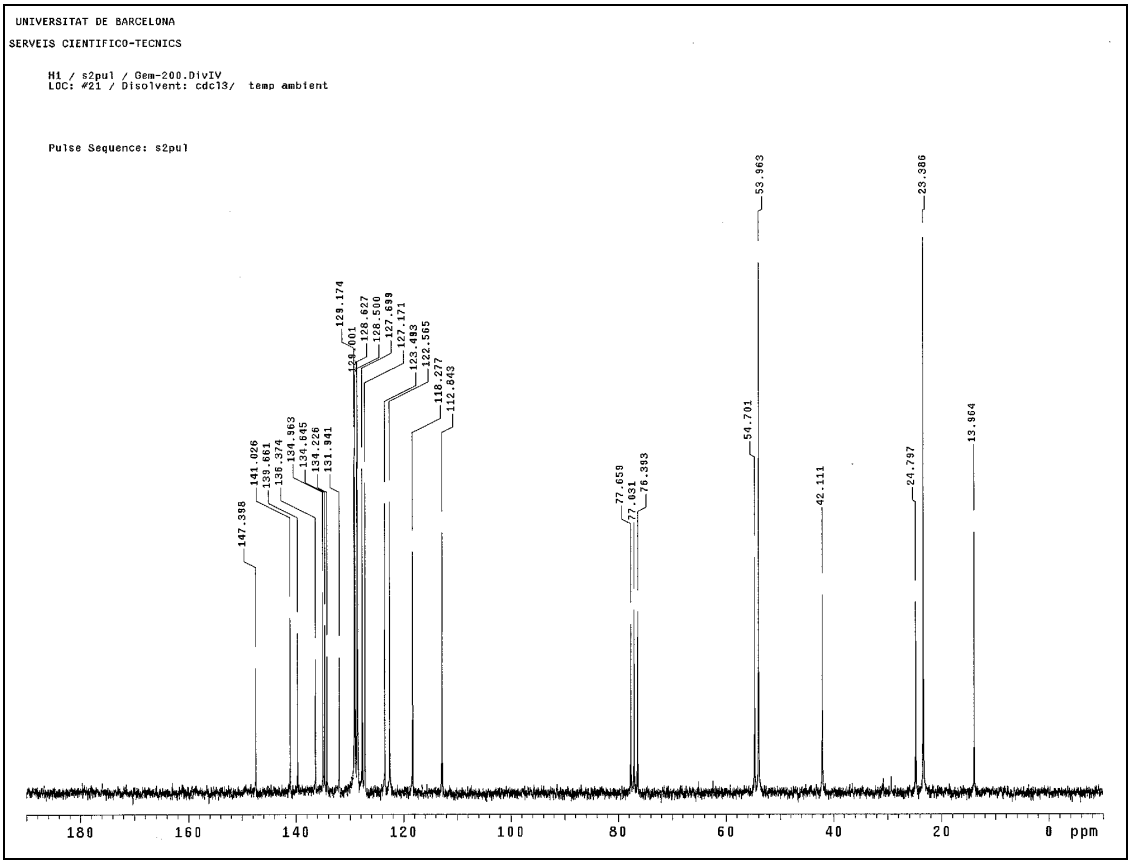


- ***N*-[2-Methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]naphthalene-2-sulfonamide 14**

^{1}H NMR (200 MHz, $CDCl_3$)

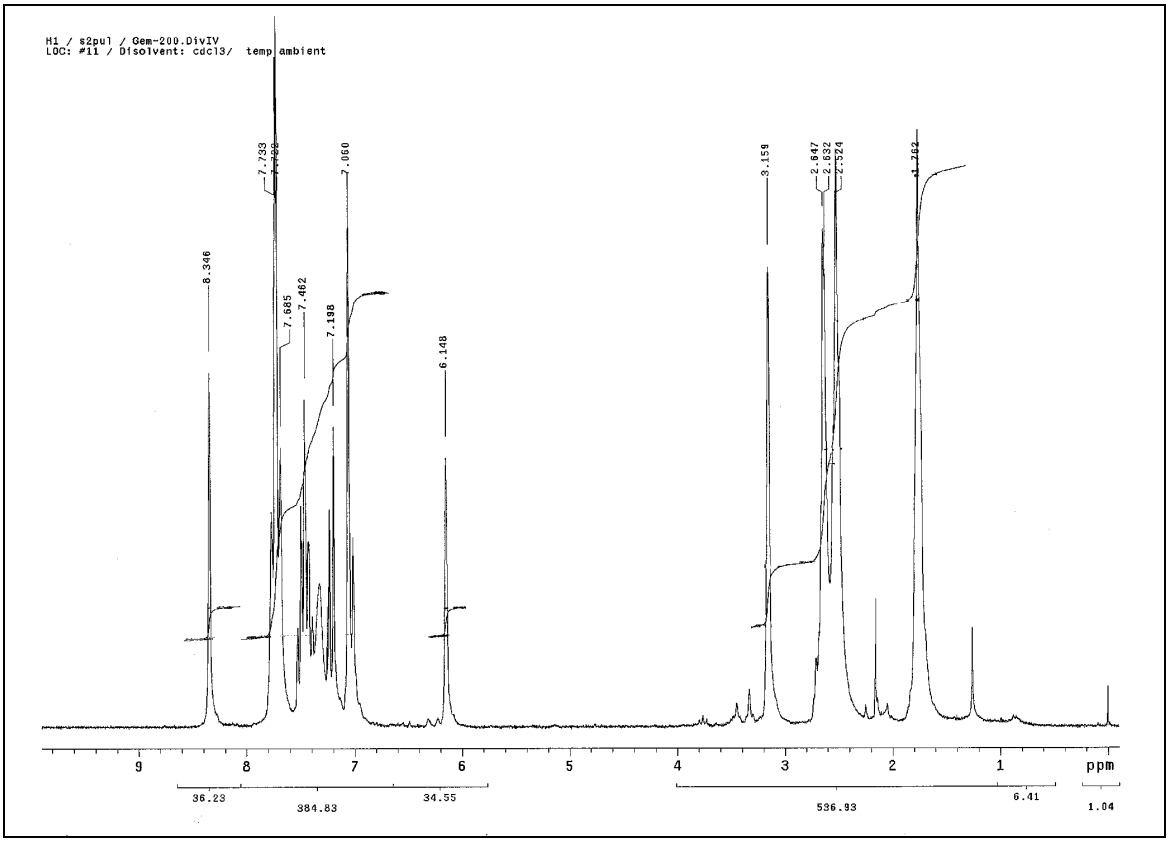


^{13}C NMR (50.3 MHz, $CDCl_3$)

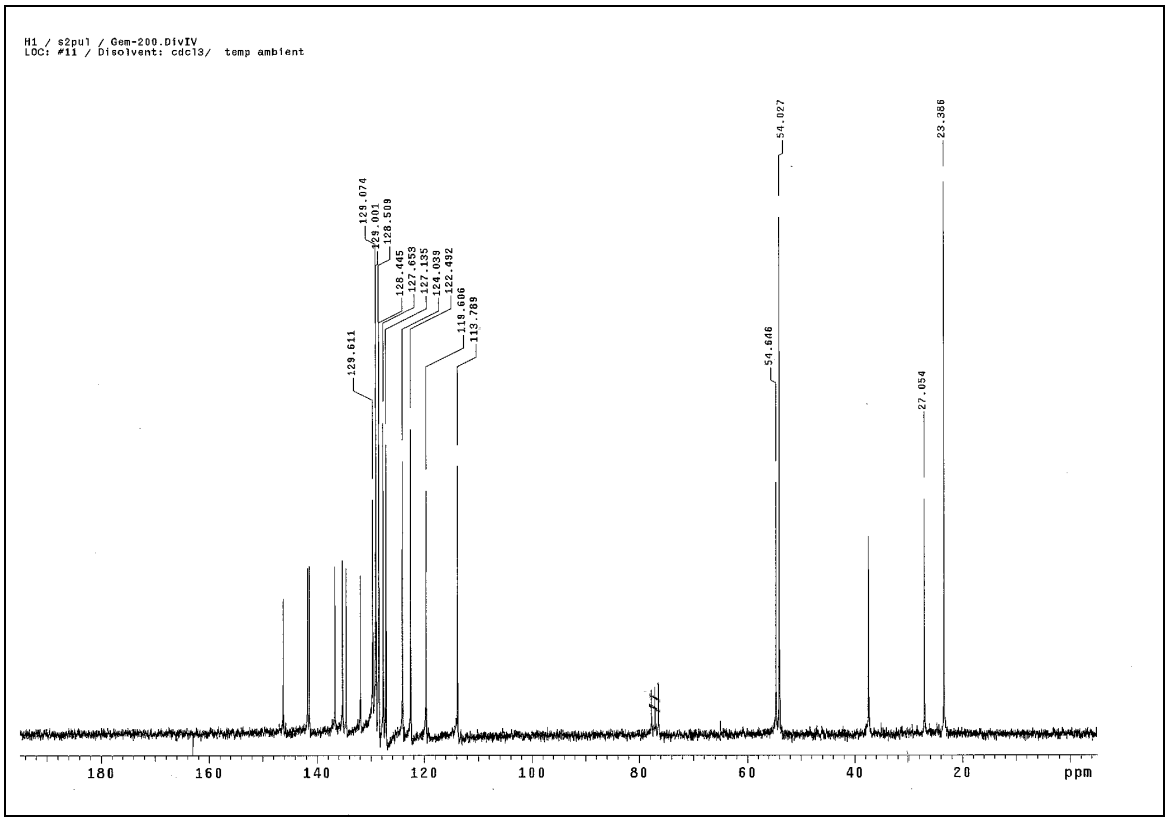


- ***N*-[3-(2-Pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]naphtalene-2-sulfonamide 15**

^{1}H NMR (200 MHz, $CDCl_3$)

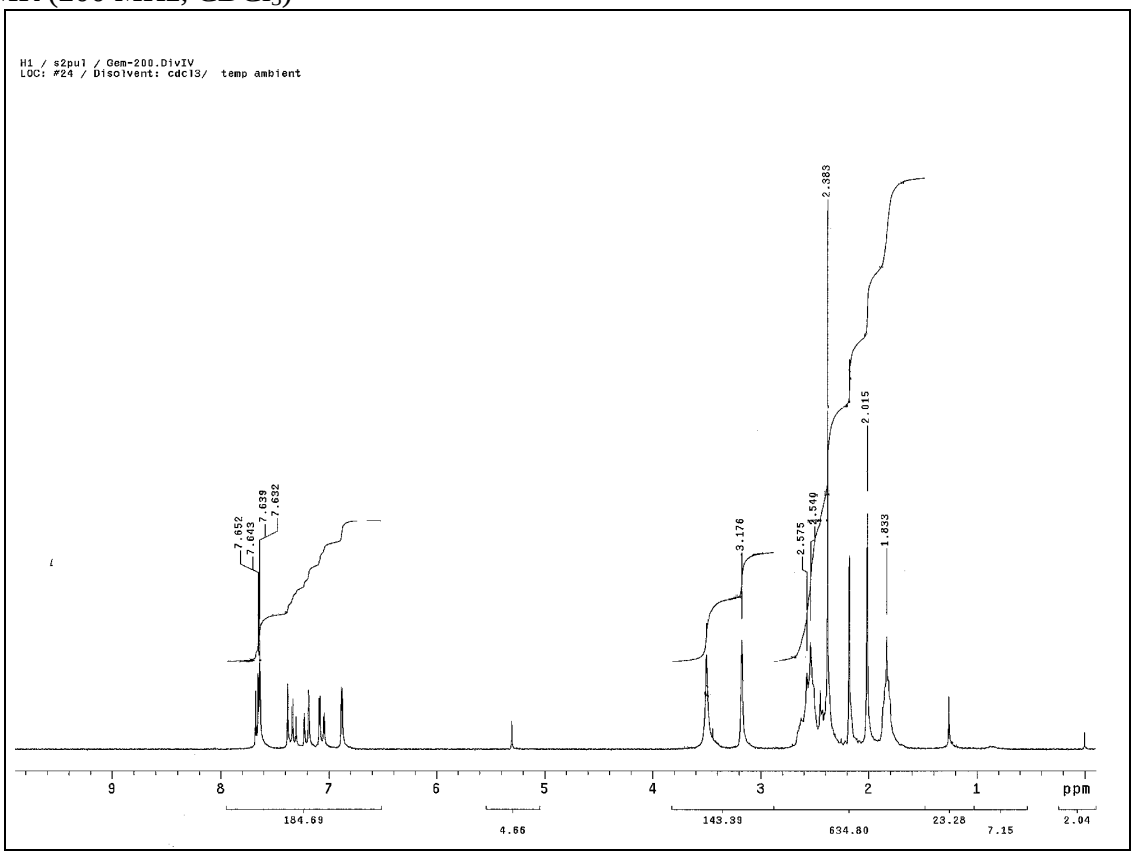


^{13}C NMR (50.3 MHz, $CDCl_3$)

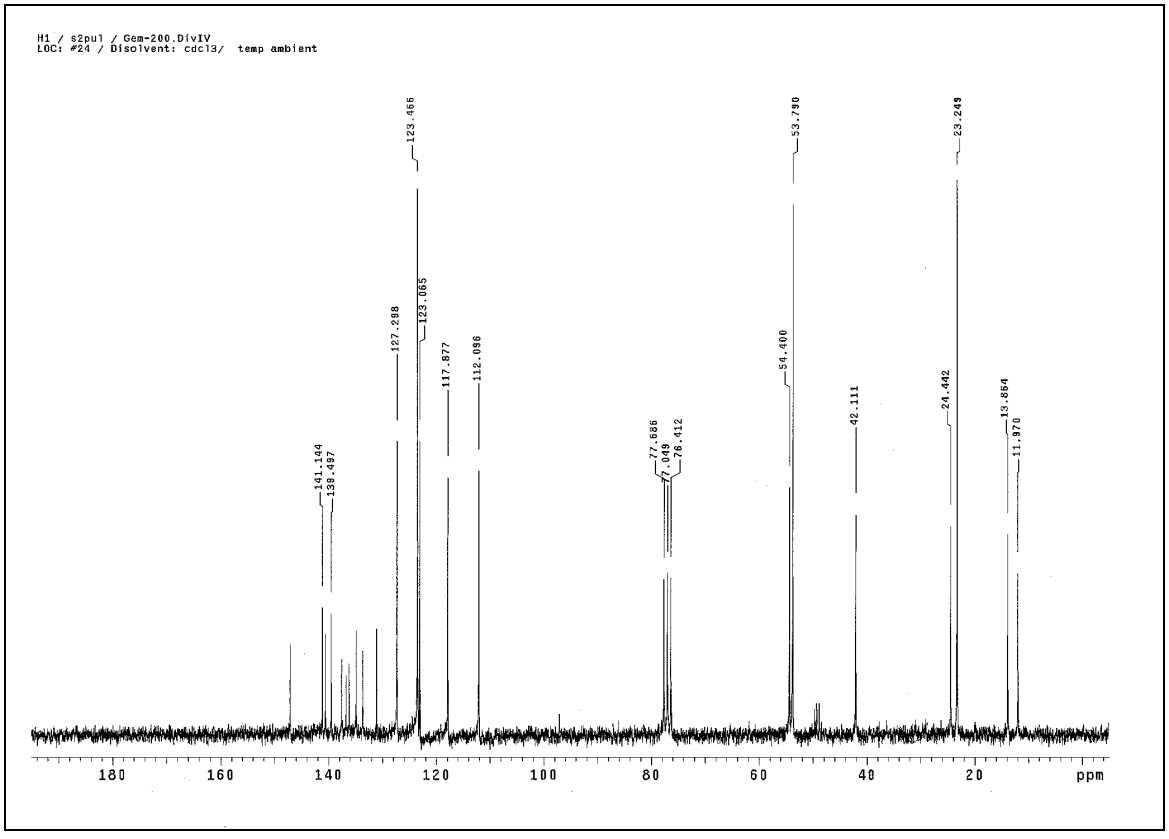


- **5-Chloro-3-methyl-*N*-[2-methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]-1-benzothiophene-2-sulfonamide 16**

^{1}H NMR (200 MHz, $CDCl_3$)

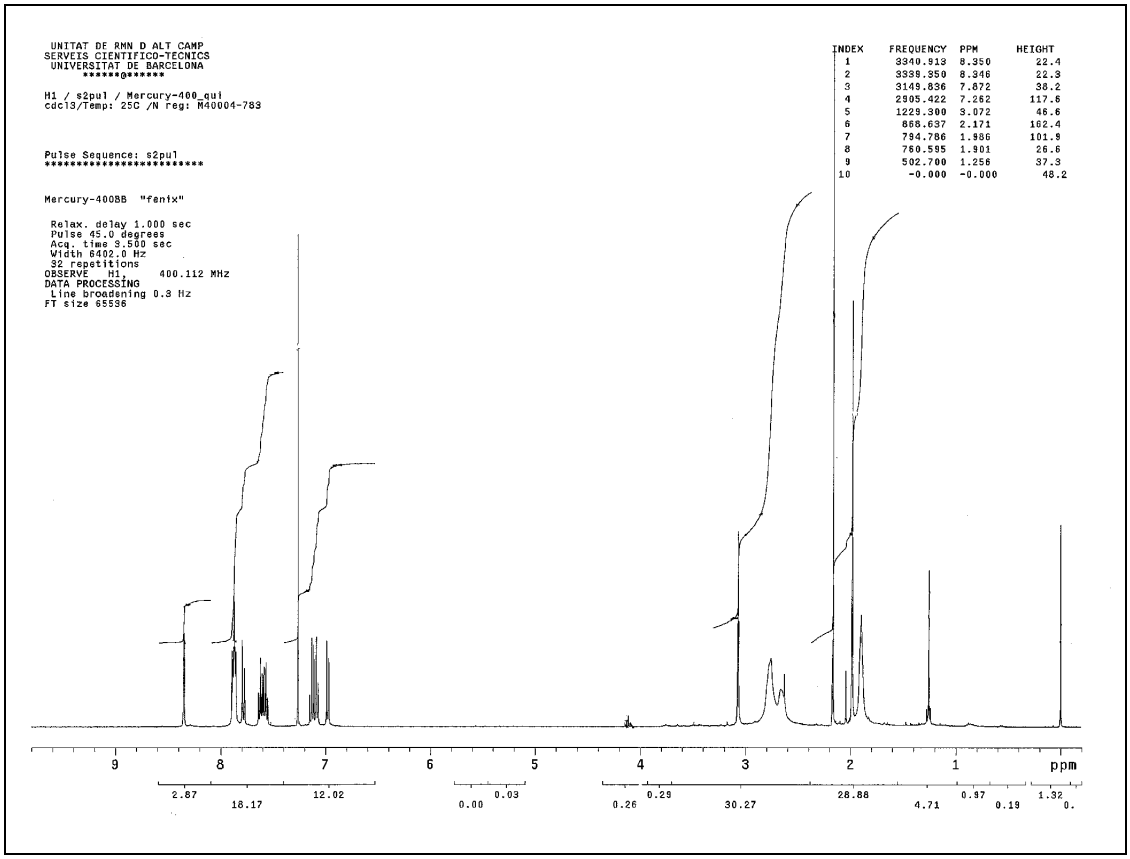


^{13}C NMR (50.3 MHz, $CDCl_3$)

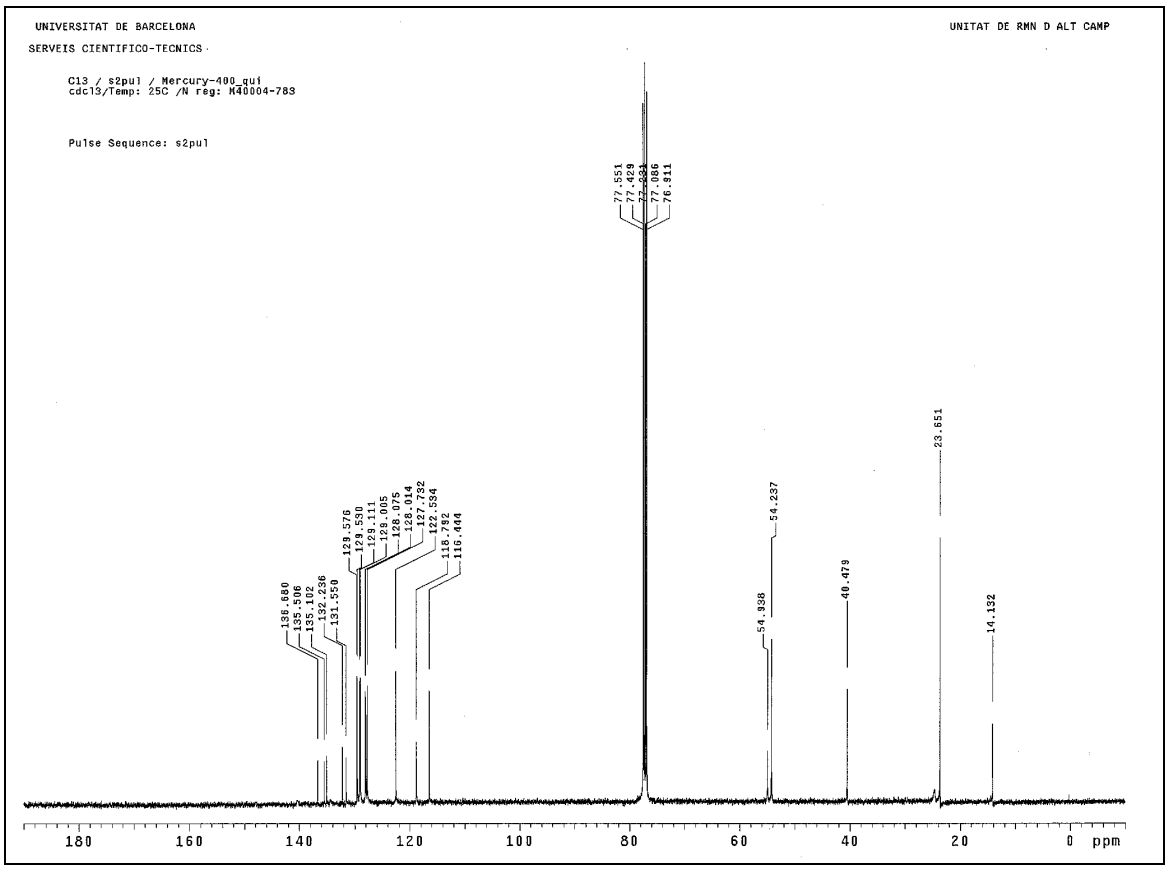


- ***N*-[2-Methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-7-yl]naphthalene-2-sulfonamide 17**

^{1}H NMR (400 MHz, $CDCl_3$)

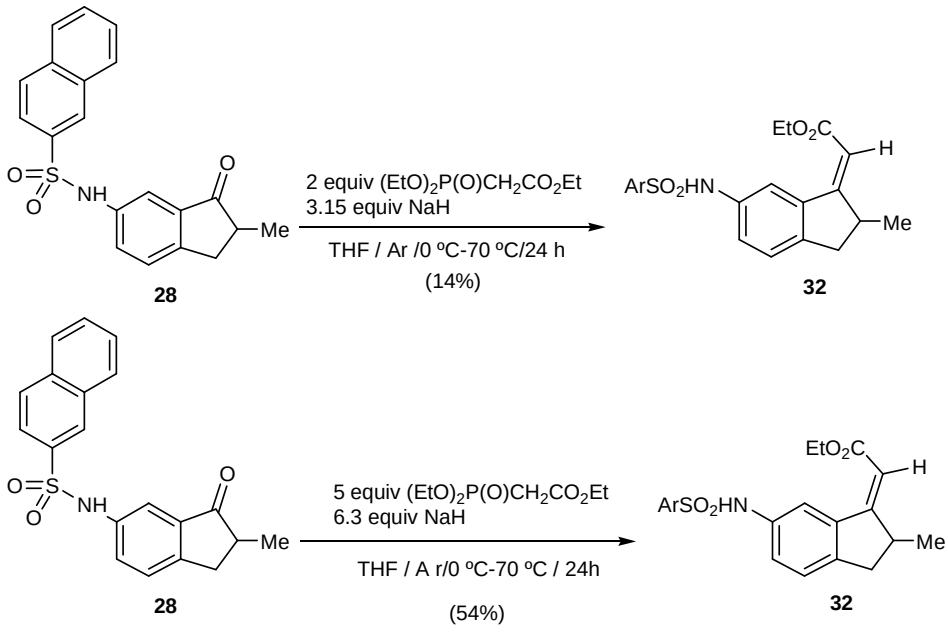


^{13}C NMR (100.6 MHz, $CDCl_3$)

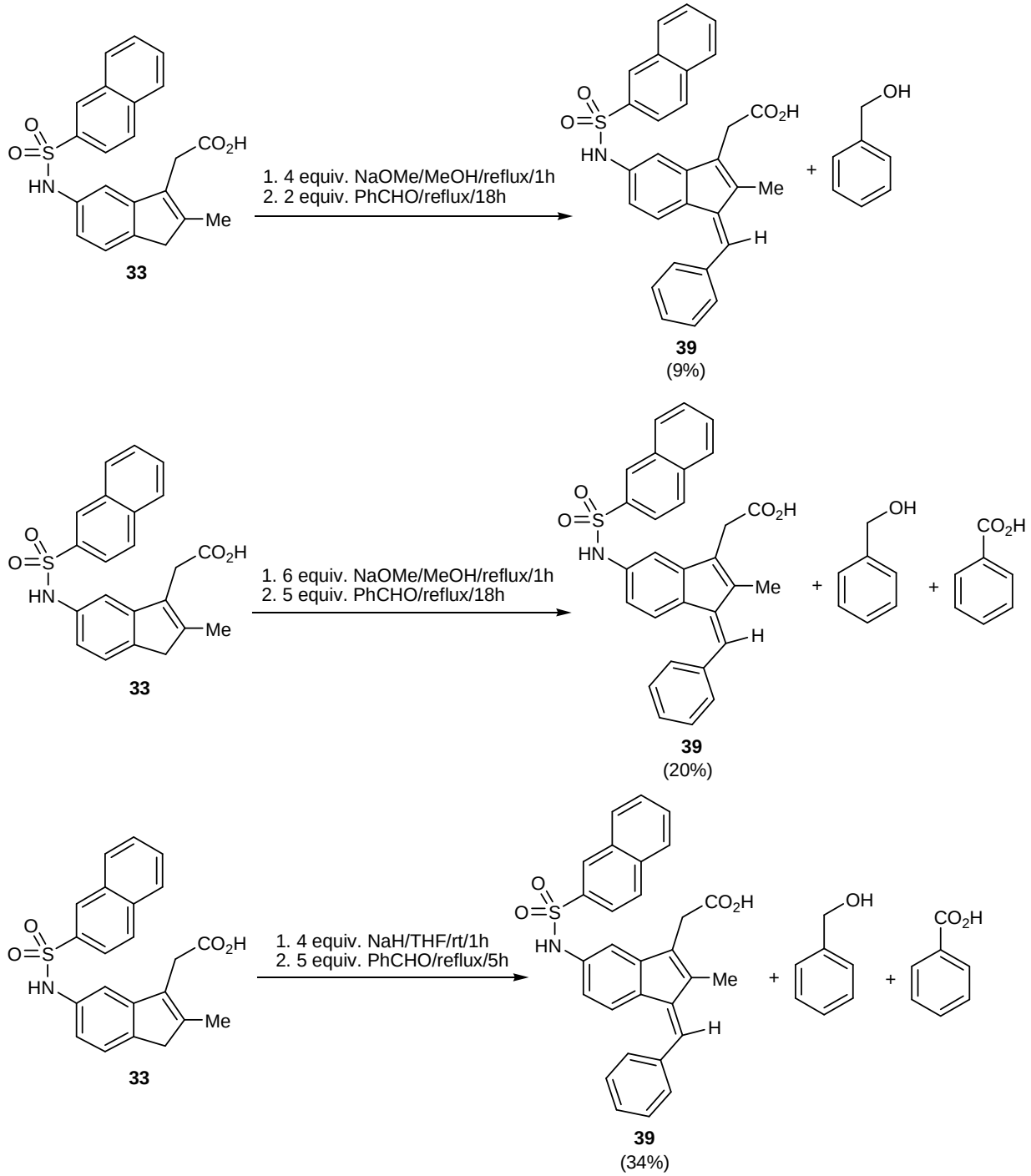


❖ ASSAYS RELATED WITH THE PREPARATION OF INDENES 12 AND 13

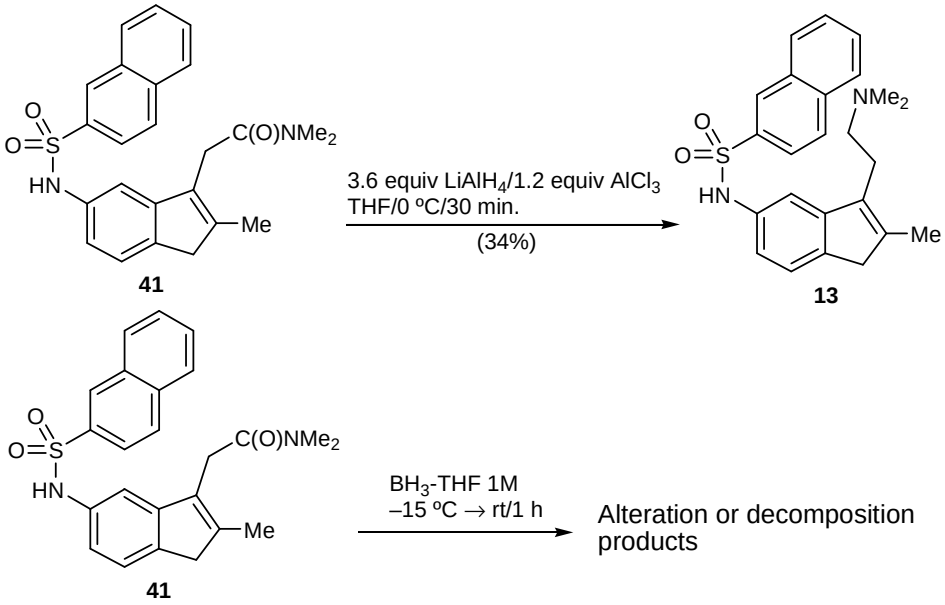
- **Ethyl {2-methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetate 32**



- **{(1*Z*)-1-Benzylidene-2-methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetic acid 39**



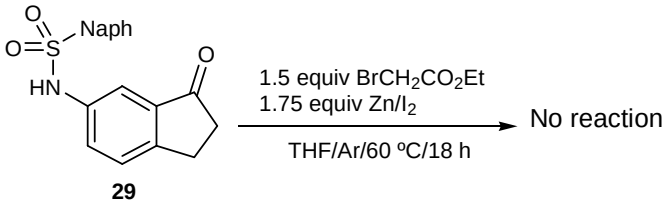
- ***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 13**



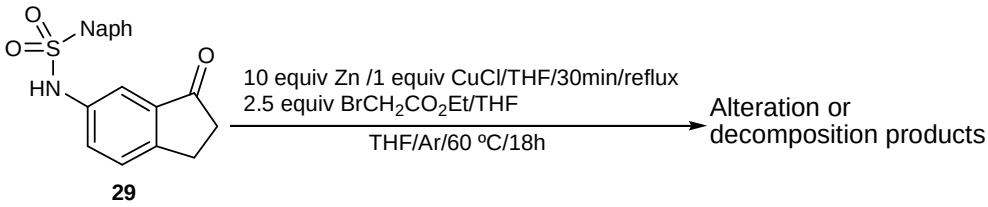
❖ ASSAYS RELATED WITH THE PREPARATION OF INDENES 14–17

- **Assays related with the transformation of indanone sulfonamide 29 to ethyl acetates 34 and 35 and acetic acid 36**

  - **Reformatsky reaction**

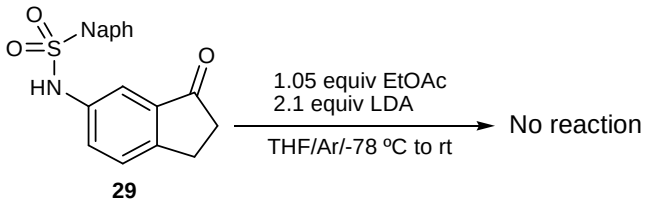


29



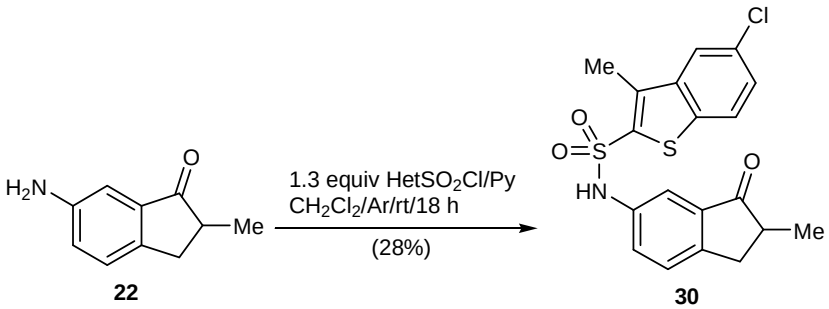
29

  - **Aldol-type condensation**

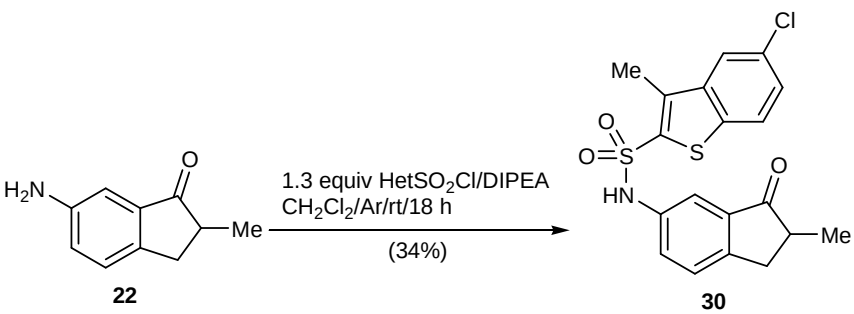


29

- **Assays related with the preparation of indanone sulfonamide 30**

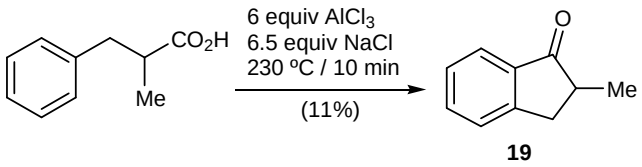


22 **30**

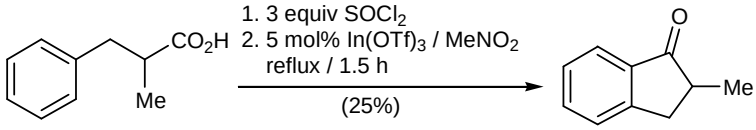


22 **30**

❖ ASSAYS RELATED WITH THE PREPARATION OF 2-METHYLINDAN-1-ONE 19



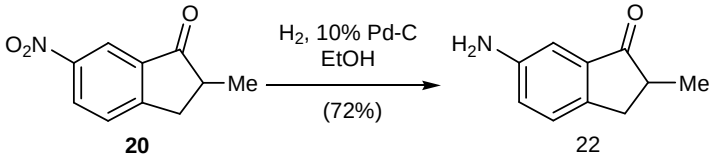
19



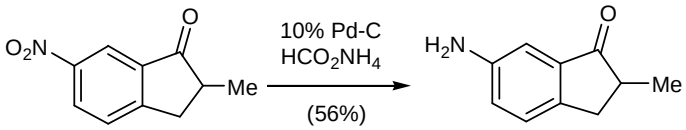
19

❖ ASSAYS RELATED WITH THE PREPARATION OF AMINOINDANONE 22

- **6-Amino-2-methylindan-1-one 22**



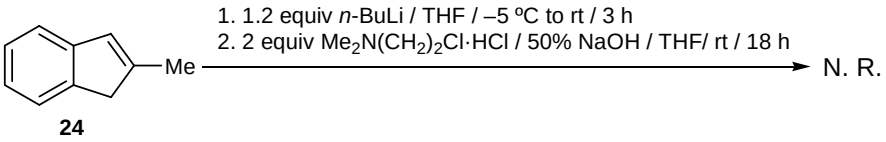
20 22



20 **22**

❖ ASSAYS RELATED WITH THE PREPARATION OF INDENE 25

- ***N*,*N*-Dimethyl-2-(2-methyl-1*H*-inden-3-yl)ethanamine 25**



24

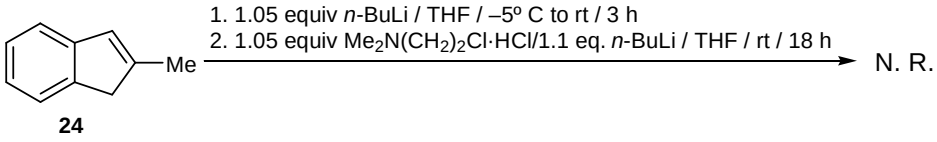


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Table S1 5-HT_6 Serotonin receptor affinity of compounds **8–17** and functionality of **12** and **13**.

Cpd.	% Inhib. @ 1 μM	K_i (nM)	E_{max}[a] (%)	I_{max}[b] (%)	cAMP production
8	3.6				
9	19.4				
10	22.3				
11	6.5				
12	91.8	216.5	89.5	1.5	Agonist
13[c]	99.6	50.6	98.3	1.8	Agonist
14	91.7	62.9	64.9	10.1	
15	91.4	46.3	76.9	11.4	
16	100.0	20.2	77.7	9.9	
17	72.5	157.5	–0.4	6.7	

[a]Agonism was expressed as E_{max}. [b]Antagonism was expressed as I_{max}. [c]% Inhib. @ 100 nM = 70.9, % Inhib. @ 10 nM = 18.9.