
# Contribució a l'Estudi dels Receptors de Serotonina. Molècules Basades en Indens i Indans

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

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A series of novel indene derivatives designed by a scaffold selection gave access to several examples of (*Z*)-arylmethylideneindenes and indenylsulfonamides that acted as serotonin 5-$HT_6$ receptor ligands. Different synthetic multistep routes could be applied to these target compounds, each with their own complexity and limitations. A reasonable route involved the (3-indenyl)acetic acids as the key intermediates, and two alternatives were also examined. The first protocol used was a two-step sequence employing a modified Horner–Wadsworth–Emmons reaction, but better results were obtained with a procedure based on the condensation of indanones with the lithium salt of ethyl acetate, followed immediately by dehydration with acid and hydrolysis/isomerization under basic catalysis. (3-Indenyl)acetic acids were transformed to the corresponding acetamides, which were effectively reduced to indenylsulfonamides **13–17** using an optimized procedure with $AlH_3$–$NMe_2Et$. The binding at the 5-$HT_6$ receptor was with moderate affinity ($K_i$ = 216.5 nM) for the (*Z*)-benzylideneindenylsulfonamide **12** and enhanced affinity for the simple indenylsulfonamide counterpart **13** ($K_i$ = 50.6 nM). Selected indenylsulfonamides **14–17** were then tested, showing $K_i$ values as low as 20.2 nM.

## Introduction

A survey of biologically active (*Z*)-stilbenes shows that (*Z*)-aryl(heteroaryl)methylideneindenes **1** form an ensemble of compounds with a variety of pharmacological profiles.[1] Relevant examples are the nonsteroidal anti-inflammatory drug (NSAID) sulindac **2** together with sulindac sulfone **3** and sulindac-derived compounds **4** (Fig. 1).[2] Exisulind **3** is a new class of targeted and pro-apoptopic drug, being the lead compound in a series of selective apoptotic antineoplasic drugs. A library of sulindac analogs **4** have led to new inhibitors of the tumor-relevant Ras signal transduction pathway, underlining the advantage of using biologically prevalidated compound classes in chemical biology research.[3,4] In an interesting study carried out concurrently with our own, Glennon and co-workers have examined the binding of several isotriptamines and indenes at the h5-$HT_6$ serotonin receptor, such as (*E*)-benzylideneindene **5** ($K_i$ = 57 nM), (benzylindenyl)ethanamine **6** ($K_i$ = 3 nM) and isotryptamine analog **7** ($K_i$ = 32 nM), revealing that the indolic nitrogen atom is not essential for binding.[5]

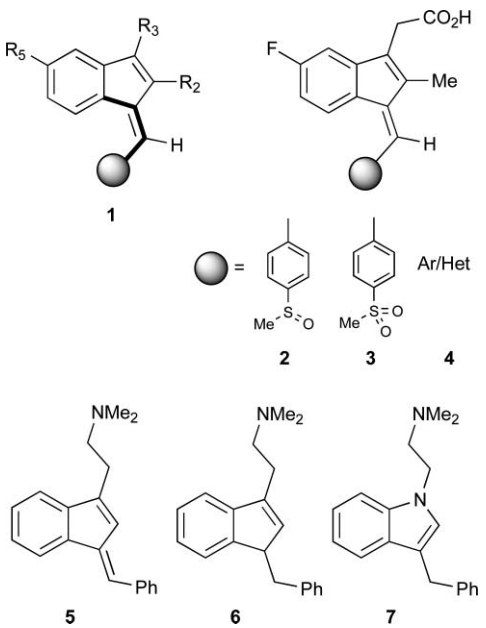


**Fig. 1**

As part of a project aimed at the study of (*Z*)-stilbenes with potential biological effects on the central nervous system (CNS), we focused our attention on an indene core of general type **1**, since indenes constitute a source of pharmacologically active molecules, and their synthesis and pharmacology have not yet been extensively explored. We thus hoped to maximise the likelihood of discovering compounds with biological properties. On the basis of these premises, the first series of indene compounds was based on the *cis*-indene structure **1** in which the (*Z*)-stilbene moiety was embedded and the traditional *N*,*N*-dimethylaminoethyl CNS functionality was incorporated at the 3-position. (*Z*)-Aryl(heteroaryl)methylideneindenes **8–11** were synthesized and compounds **10** and **11** were profiled against a panel of 64 radioligand binding assays along with the 5-$HT_6$

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† Electronic supplementary information (ESI) available: $^1H$ NMR and $^{13}C$ NMR assignments, NMR spectra of targeted compounds, assays related to the preparation of compounds **12–17**, **19**, **22** and **25**, and 5-$HT_6$ binding affinity and functionality (Table S1). See DOI: 10.1039/b808641a

serotonin receptor, but none of them showed significant binding affinities (Scheme 1).

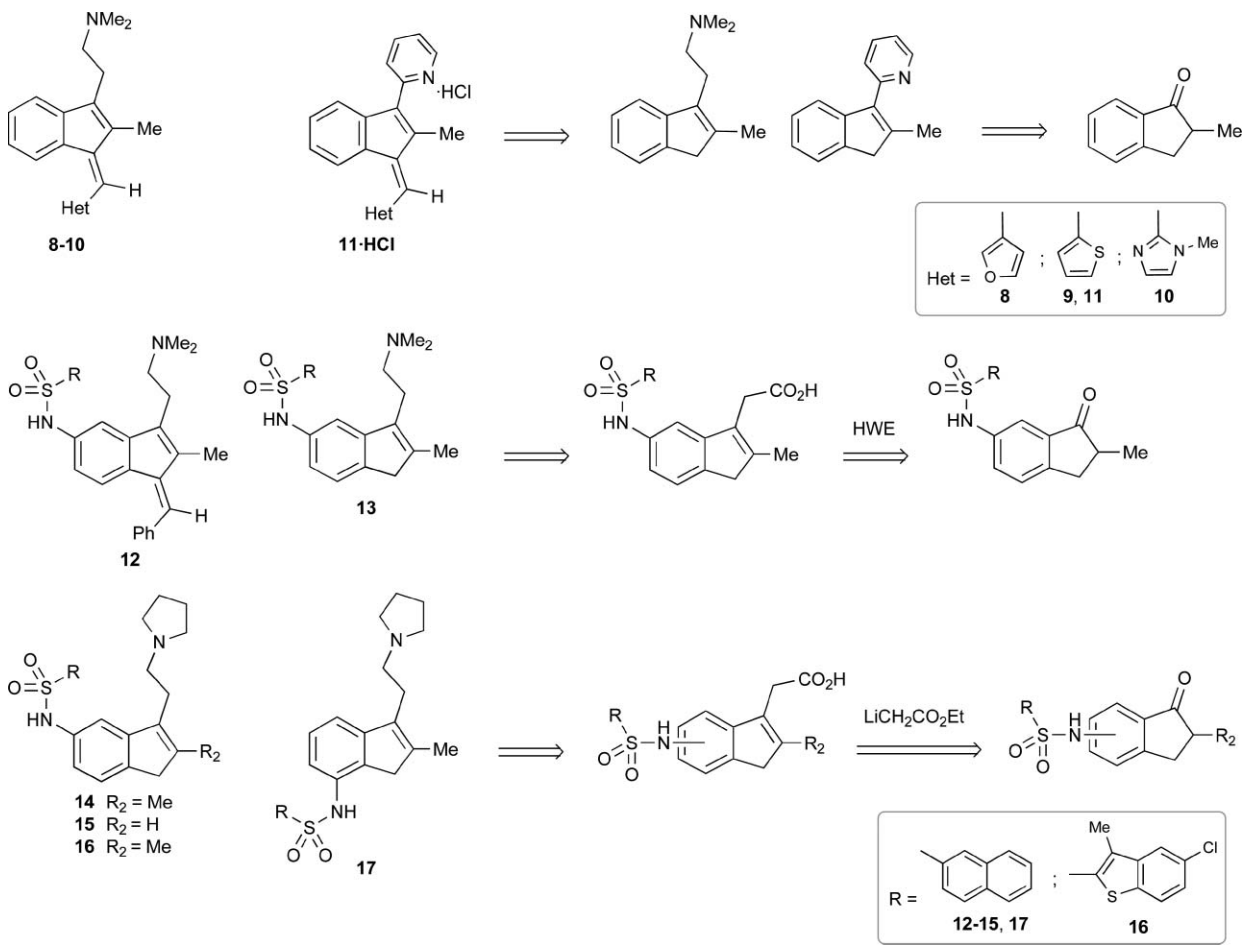
The subsequent design step was namely the incorporation of a sulfonamide group at the 5-position of the indene ring, since studies of 5-$HT_6$ serotonin receptor ligands have highlighted the importance of the sulfonyl moiety (*e.g.* sulfonamides, sulfones) for binding,[6] such as the series of indole-based sulfonamides developed by Esteve Laboratories, *e.g.* the indolylsulfonamide E-6837.[7–9] Accordingly, (*Z*)-benzylideneindenylsulfonamide **12** and the simple indenylsulfonamide counterpart **13** were prepared, and the binding was with moderate affinity ($K_i$ = 216.5 nM) for **12** and significant affinity for **13** ($K_i$ = 50.6 nM). Selected reduced indenylsulfonamides **14–17** were then synthesized and exhibited binding affinity with $K_i$ values ≥20.2 nM.

A relevant parameter playing a crucial role in a scaffold selection process concerns the scaffold synthetic accessibility and the ease with which its derivatives can be prepared. Despite the utility of indenes in drug discovery and development, along with metallocene-based catalysis, *e.g.* olefin polymerization, their complexity means that synthetic approaches have been far less investigated than in the case of heteroaromatic compounds such as indoles.[10] Reasonable retrosynthetic routes to target indene models **8–17** are shown in Scheme 1, proceeding from either 2-methylindan-1-one or indan-1-one sulfonamides. The presence of a methyl group at the 2-position of the core ring should favor the formation of both the (*Z*)-diastereoisomers of **8–12** and the desired *endo*-olefin of the key indenylacetic acids in the preparation of indenylsulfonamides **13–14** and **16–17**.

## Results and discussion

### Chemistry

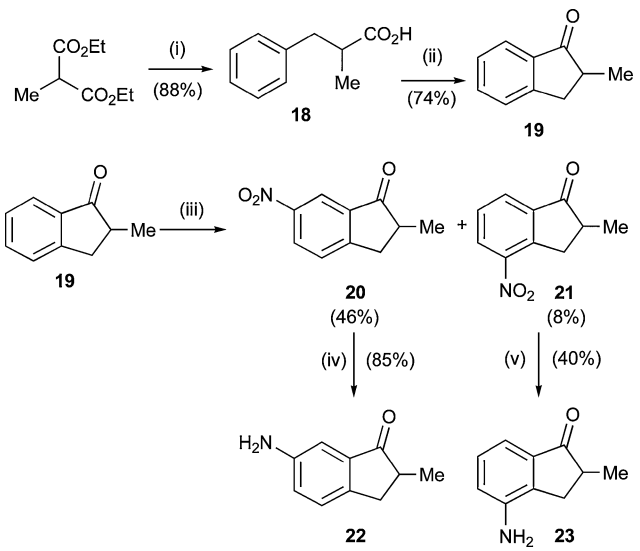
According to the retrosynthetic analysis of Scheme 1, the two types of target indene derivatives, (*Z*)-aryl(heteroaryl)methylideneindenes **8–12** and indenylsulfonamides **13–17**, could be prepared using multistep routes starting from substituted indanones. Thus, methylindanone was transformed to both indenylethanamine or indenylpyridine intermediates and a subsequent reaction with an aromatic/heteroaromatic aldehyde, using a Knoevenagel condensation, afforded the (*Z*)-arylmethylideneindenes **8–11**, whereas multistep routes were required for indenylsulfonamides **12–17**. Two alternatives were examined for the synthesis of the key (3-indenyl)acetic acids: the first protocol was a two-step sequence involving the Horner–Wadsworth–Emmons reaction (HWE) but better results were obtained with an efficient procedure based on the condensation of indanones with the lithium salt of ethyl acetate.




**Scheme 1** Retrosynthetic pathways to the target (*Z*)-aryl(heteroaryl)methylideneindenes **8–12** and indenylsulfonamides **13–17**.

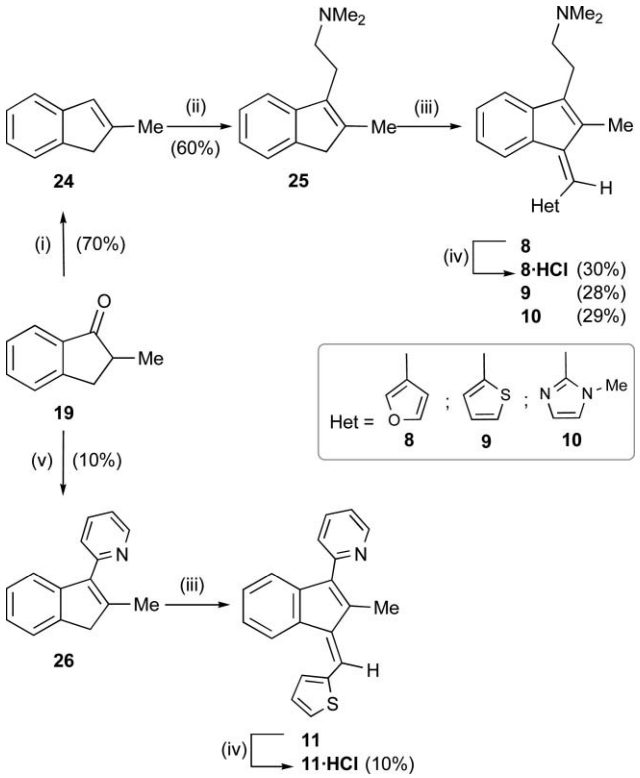
Preparation of substituted indan-1-ones started with a malonic-ester acid synthesis that gave the propanoic acid **18**, which was converted to the corresponding acid chloride and cyclized to 2-methylindan-1-one **19** under Friedel–Crafts reaction conditions (see ESI†). Nitration of **19** gave a mixture of nitroindan-1-one isomers **20** and **21** in 46% and 8% yield, respectively (Scheme 2). Catalytic hydrogenation of nitroindanones **20** and **21** gave the corresponding aminoindanones **22** and **23** in 72% and 40% yield, but when the reduction was scaled up to 35 mmol the yield decreased. After trying different reducing agents and reaction conditions, the best result for the reduction of **20** was achieved by treatment with iron in aqueous acetic acid. The amino derivative **22** was afforded in good yield (85%), and could be scaled up to 40 mmol (see ESI).




**Scheme 2** Synthesis of aminoindan-1-ones. *Reagents and conditions*: (i) (a) Na, EtOH, rt, (b) $PhCH_2Br$, reflux, (c) KOH, $H_2O$, reflux, (d) 170 °C; (ii) (a) $SOCl_2$, reflux, (b) $AlCl_3$, toluene, reflux; (iii) $KNO_3$, $H_2SO_4$, −5 °C; (iv) Fe, AcOH–$H_2O$, 90 °C; (v) $H_2$, 10% Pd/C, EtOH, rt.

Compounds **8–10** were prepared from indanone **19** following the three-step sequence shown in Scheme 3. The crucial step was the conversion of indene **24** into (3-indenyl)ethanamine **25**, which was transformed to the (*Z*)-indenes **8–10** using a Knoevenagel condensation with various aromatic/heteroaromatic aldehydes, overall average yield being 12% (see ESI). A similar procedure was then applied to the synthesis of indene **11**, which began with the addition of 2-lithiopyridine to **19**, followed by dehydration with sulfuric acid to give indenylpyridine **26**. This was condensed with 2-thiophenecarboxaldehyde in the presence of NaOMe to afford (*Z*)-thienylmethylideneindene hydrochloride **11**·HCl in 1% overall yield. The purity of (*Z*)-aryl(heteroaryl)methylideneindenes **8–11** was variable due to their troublesome isolation and purification, chromatographic separations being necessary in all cases.

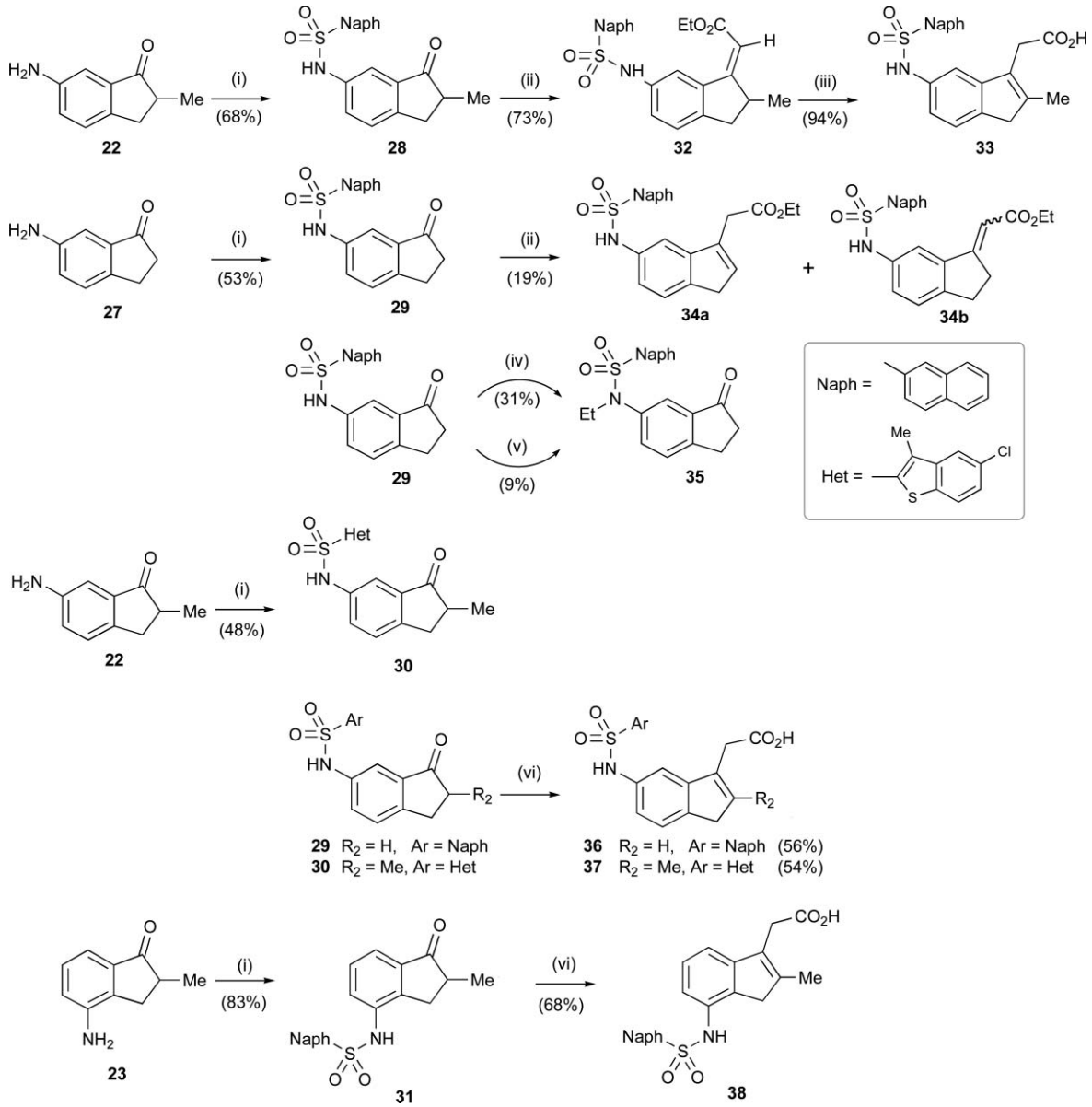
Although different multi-step synthetic routes could be applied to the target indenylsulfonamides **12–17**, a reasonable pathway appeared to involve (3-indenyl)acetic acids as the key intermediates (Scheme 1). Accordingly, preparation of the acetic acid derivatives started with the reaction of aminoindanones **22**, **27** and **23** with the corresponding aryl(heteroaryl)sulfonyl chlorides, giving the corresponding indanone sulfonamides **28–31** (Scheme 4).




**Scheme 3** Synthesis of (*Z*)-aryl(heteroaryl)methylideneindenes. *Reagents and conditions*: (i) (a) $NaBH_4$, THF–MeOH, rt, (b) $TsOH·H_2O$, toluene, reflux, (ii) (a) *n*-BuLi, THF, −5 °C, (b) $Me_2N(CH_2)_2Cl·HCl$, rt; (iii) (a) NaOMe, MeOH, 0 °C, (b) HetCHO, MeOH, reflux; (iv) HCl, $Et_2O$; (v) (a) 2-bromopyridine, *n*-BuLi, $Et_2O$, −60 °C, (b) 95–97% $H_2SO_4$, 0 °C.

As a starting point, the Horner–Wadsworth–Emmons reaction was used to transform **28** into ethyl (*Z*)-indanylacetate **32**, and after examining various conditions, the reaction was improved by increasing the amounts of sodium hydride to 11.5 equivalents and triethyl phosphonoacetate to 10 equivalents, which led to olefin **32** in 73% yield (Scheme 4). Hydrolysis and isomerization of **32** under basic catalysis afforded the key (3-indenyl)acetic acid **33** in 94% yield. The optimized Horner–Wadsworth–Emmons protocol was then employed to indanone sulfonamide **29** to give a mixture of ethyl acetates **34a** and **34b** in very low yield (19%), showing that the HWE reaction was clearly less efficient. Changing the basic conditions,[11a,b] the isomeric acetates **34a** and **34b** were not formed and the *N*-ethyl-*N*-indan-1-one sulfonamide **35** was produced instead, probably due to the presence of LiBr and $LiOH·H_2O$,[11c] respectively (Scheme 4).

In consequence, an alternative method appeared to be the addition of organometallic compounds to indanones. We first tried the Reformatsky reaction between indanone sulfonamide **29** and an ester-stabilized organozinc reagent ($BrZnCH_2CO_2Et$) but this proved to be ineffective (see ESI). We then examined an aldol-type condensation with indanone sulfonamide **29** using the lithium salt of ethyl acetate, immediately followed by dehydration with trifluoroacetic acid and hydrolysis/isomerization with NaOMe in methanol, (3-indenyl)acetic acid **36** being obtained in an acceptable yield of 56% (see Scheme 4 and ESI). Applying the same experimental procedure, indanone sulfonamides **30** and **31**




**Scheme 4** Synthesis of (3-indenyl)acetic acids **33**, **36**, **37** and **38**. *Reagents and conditions*: (i) $RSO_2Cl$, pyridine, $CH_2Cl_2$, rt; (ii) 10 equiv $(EtO)_2P(O)CH_2CO_2Et$, 11.5 equiv NaH, THF or DME, 0 °C → reflux; (iii) NaOMe, MeOH, reflux; (iv) 10 equiv $(EtO)_2P(O)CH_2CO_2Et$, 12 equiv LiBr, 11.5 equiv $Et_3N$, DME, reflux; (v) 10 equiv $(EtO)_2P(O)CH_2CO_2Et$, 4 Å MS, 11.5 equiv $LiOH{\cdot}H_2O$, THF, reflux; (vi) (a) EtOAc, LHMDS, THF, −78 °C, (b) TFA, $CH_2Cl_2$, −5 °C, (c) NaOMe, MeOH, reflux.

were transformed to the corresponding (3-indenyl)acetic acids **37** and **38** in good yields.

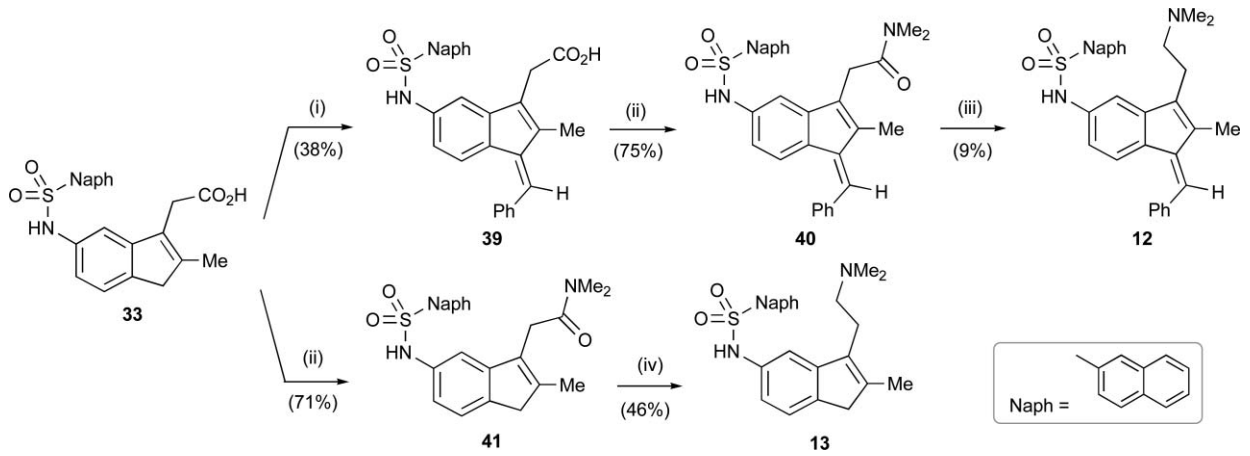
Knoevenagel condensation between (3-indenyl)acetic acid **33** and benzaldehyde in the presence of NaH yielded (*Z*)-benzylideneindene acetic acid **39** along with by-products from the Cannizzaro reaction (see ESI). Compound **39** was transformed to the corresponding indenylacetamide **40** and the amide group was reduced with $LiAlH_4$ in THF to give the target (*Z*)-benzylideneindenylsulfonamide **12** in a very low overall yield of 7% (Scheme 5). In a similar manner, the simpler indenylsulfonamide counterpart **13** was prepared starting from indenylacetic acid **33**, which was transformed to indenylacetamide **41**. After changing the reducing agent to $AlH_3$–$NMe_2Et$ in THF, acetamide **41** was transformed to **13** in acceptable 33% overall yield.

Following a similar stepwise synthetic route, indenylsulfonamides **14–17** were obtained from the corresponding (3-indenyl)-acetic acids **33** and **36–38** as shown in Scheme 6. Thus, compounds **33** and **36–38** were transformed to the corresponding amides **42–45**, which were effectively reduced to the target indenes **14–17** with $AlH_3$–$NMe_2Et$, overall yields ranging from 13% to 40%.

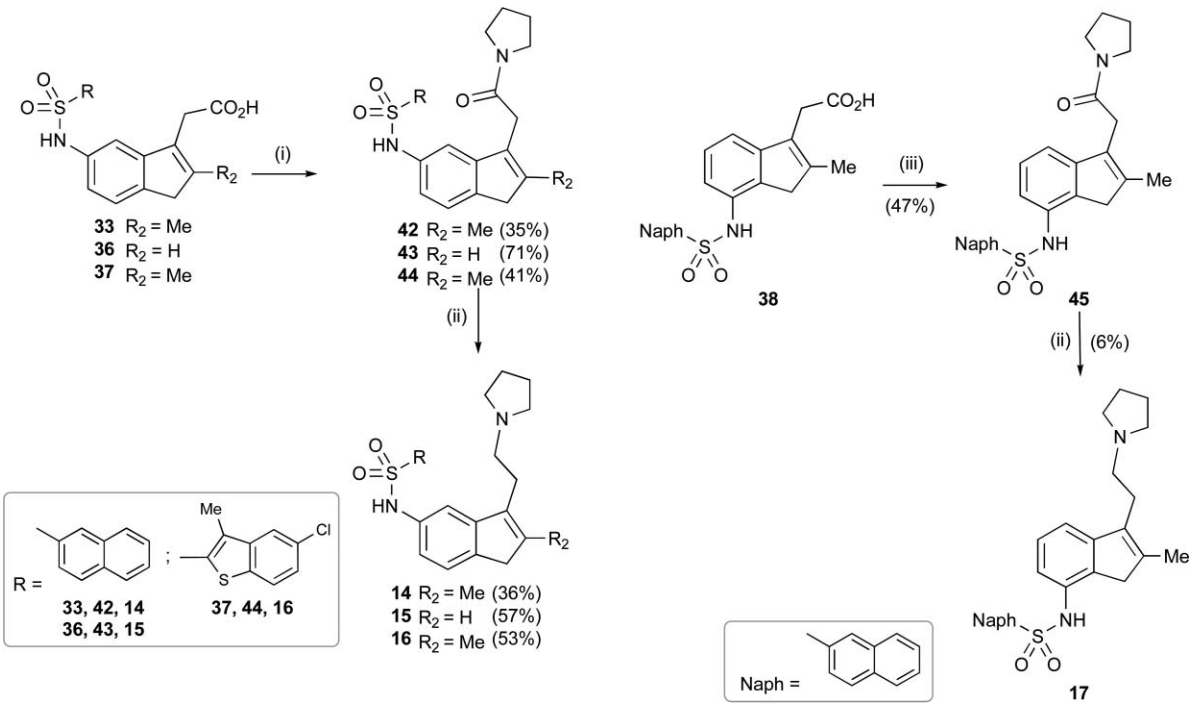
Depending on the difficulties encountered in the isolation and purification, the purity of the indenylsulfonamides **13–17** was variable but sufficient for the preliminary testing of their affinity for the 5-$HT_6$ serotonin receptor. Among them, compound **16**, which had a good affinity for the 5-$HT_6$ receptor, showed a purity of 99.6% by HPLC.

Finally, incorporation of a sulfonamide moiety into the above-mentioned (benzylindenyl)ethanamine **6**, with a high affinity




**Scheme 5** *Reagents and conditions*: (i) (a) NaH, THF, rt, (b) PhCHO, reflux; (ii) (a) 1,1′-carbonyldiimidazole, THF, rt, (b) $Me_2NH$, THF, rt; (iii) $LiAlH_4$, THF, rt → reflux; (iv) $AlH_3$–$NMe_2Et$, THF, 0 °C.



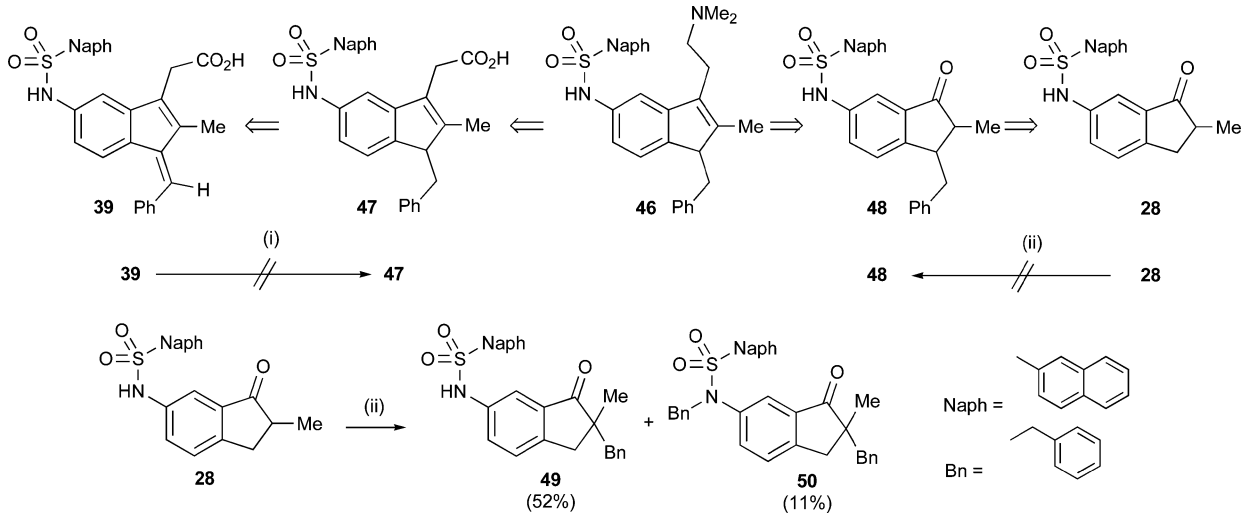

**Scheme 6** *Reagents and conditions*: (i) (a) 1,1′-carbonyldiimidazole, THF, rt, (b) pyrrolidine, THF, rt; (ii) $AlH_3$–$NMe_2Et$, THF, 0 °C or rt; (iii) (a) $SOCl_2$, $CH_2Cl_2$, reflux, (b) $C_4H_8NH$, $CH_2Cl_2$, rt.

to the 5-$HT_6$ receptor,[5] led to (benzylindenyl)sulfonamide **46**, a structurally similar model that could allow us to examine the contribution of a sulfonamide moiety. Attempts were made to prepare sulfonamide **46** either from (*Z*)-benzylideneindene acetic acid **39** or from indanone sulfonamide **28**, but the results were unsuccessful (Scheme 7). Catalytic hydrogenation of (*Z*)-benzylideneindene **39** gave products of decomposition, and treatment of indanone sulfonamide **28** in a manner similar to that reported by Trost and Latimer[11d] did not provide 3-benzylindan-1-one **48**, but benzylindanones **49** and **50**, and these were not further investigated.

The structures of the new compounds were confirmed by spectroscopic methods (see Experimental and ESI). The (*Z*)-configurations of the target indenylidenes **8–12** was confirmed by NOE studies. For example, irradiation of the methyl protons of the indene core and the methyl protons of the imidazole ring in compound **10** gave an NOE for the olefinic proton, confirming the (*Z*)-configuration (Fig. 2).

## Biological results

(*Z*)-Aryl(heteroaryl)methylideneindenes **10** and **11**·HCl were profiled against a panel of 64 radioligand binding assays, at a compound concentration of 10 μM,[12] and the binding affinities were found not to meet criteria significant for the context of the present study. At a micromolar level, the human 5-$HT_6$ serotonin binding affinity of (*Z*)-aryl(heteroaryl)methylideneindenes **8–11**




**Scheme 7** *Reagents and conditions*: (i) $H_2$, 10% Pd/C, EtOH; (ii) (a) LDA, THF, −78 °C → rt, (b) BnBr, THF, rt.

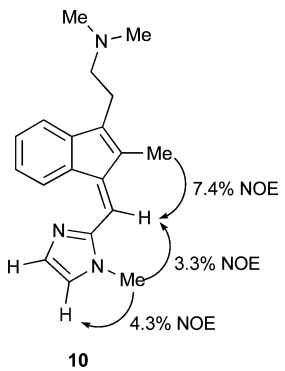



**Fig. 2**

was below 22% whereas (*Z*)-benzylideneindenylsulfonamide **12** showed an inhibition of 91.8% (see Table S1†).

The subsequent design step was an indole–indene scaffold switch based on the highly potent agonist E-6837.[7–9] Thus, indenylsulfonamides **13–17** were only tested on the 5-$HT_6$ receptor. Accordingly, incorporation of the sulfonamide moiety at the indene 5-position gave rise to an enhanced affinity for the 5-$HT_6$ serotonin receptor, as shown by the compound pairs **12** ($K_i$ = 216.5 nM) and the more simple indenylsulfonamide **13** ($K_i$ = 50.6 nM). Changing the dimethylamino group in **13** for a pyrrolidine, compound pairs **14** ($K_i$ = 62.9 nM) and **15** ($K_i$ = 46.3 nM) showed similar binding affinities (Fig. 3). Comparing the affinities of the isomer pairs inden-5-ylsulfonamide **14** ($K_i$ = 62.9 nM) and inden-7-ylsulfonamide **17** ($K_i$ = 157.5 nM) permitted us to rule out additional studies with compounds containing a sulfonamide moiety in the 7-position of the indene core. Yet when the sulfonamide substitution of a 2-naphthyl group in **14** was replaced by an heteroaryl group in **16**, the $K_i$ decreased to 20.2 nM (see Table S1†), a remarkable directing effect modulated by the nature of the aryl(heteroaryl) ring in the sulfonamide moiety.

An array of highly potent and selective 5-$HT_6$ ligands has been reported in the last few years, but the majority have been identified as antagonists. A major drawback to exploring agonists is their moderate selectivity, especially against different subtypes of

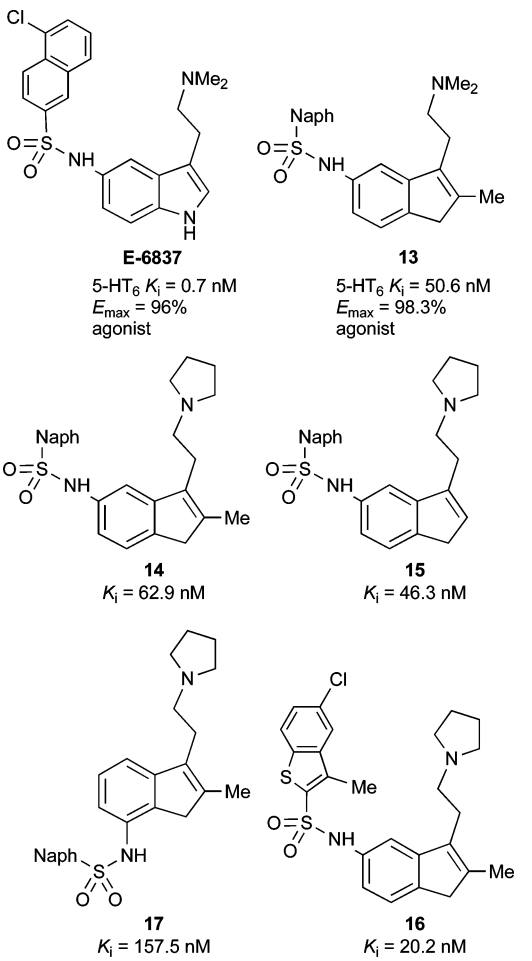



**Fig. 3** Indole–indene core change: an approach toward high affinity and selective serotonin 5-$HT_6$ receptor ligands.

5-HT serotonin receptors.[9] When indenylsulfonamides **12** and **13** were tested in the cAMP assay, their functionality was found to be that of 5-$HT_6$ receptor agonists. Notably, indenylsulfonamide **13** proved to be a full agonist, and this series presents good

potential for further development due to the utility of 5-$HT_6$ receptor agonists in the investigation of the functional role of 5-$HT_6$ receptors.

## Conclusions

A scaffold selection from several (*Z*)-arylmethylideneindenes **8–12** involving an indole–indene core change led to the identification of simple indenylsulfonamides **13–17** with good affinities at the serotonin 5-$HT_6$ receptors, showing $K_i$ values as low as 20.2 nM. We determined a convenient synthetic pathway to the target indenylsulfonamides using (3-indenyl)acetic acids as the key intermediates, and several routes were then examined. The best option to prepare the advanced intermediates was based on an aldol-type condensation between indanone sulfonamides and the lithium salt of ethyl acetate, immediately followed by dehydration with trifluoroacetic acid and hydrolysis/isomerization with NaOMe in methanol. The structural changes responsible for enhancing the 5-$HT_6$ receptor binding profile are governed by the chemical tractability of the indene-based scaffolds, and additional studies are needed for general synthetic approaches to the designed indene-based scaffold ligands. On the whole, indenylsulfonamides **13–17** appeared to be interesting for further development due to the utility of 5-$HT_6$ receptor agonists in the investigation of the functional role of 5-$HT_6$ receptors. Efforts are currently being directed towards the design and synthesis of structural analogues both closely and distantly related to the reported indenylsulfonamides in the quest for potent and selective indene-based sulfonamide ligands for 5-$HT_6$ serotonin receptors.

## Experimental

### General methods

Melting point: Gallenkamp Melting Point Apparatus MPD350. BM2.5 with digital thermometer; uncorrected. IR (KBr disks or thin film): Nicolet 205 FT or Perkin Elmer 1430 spectrophotometers. $^1$H NMR: Varian Gemini 200 (200 MHz), Varian Gemini 300 (300 MHz) and Mercury 400 (400 MHz) spectrometers at 298 K. Chemical shifts referenced and expressed in ppm ($\delta$) relative to the central peak of DMSO-$d_6$ (2.49 ppm) and TMS for chloroform-d. $^{13}$C NMR: Varian Gemini 200 (50.3 MHz), Varian Gemini 300 (75.4 MHz) and Mercury 400 (100.6 MHz) spectrometers at 298 K. Chemical shifts were referenced and expressed in ppm ($\delta$) relative to the central peak of DMSO-$d_6$ (39.7 ppm) and chloroform-d (77.0 ppm). (*Z*)-Configurations were determined by NOE difference experiments (see Fig. 2 and ESI†). MS: Hewlett-Packard spectrometer (HP-5989A model) using EI at 70 eV. ESI-HRMS: Agilent LC/MSD-TOF spectrometer. Microanalysis: Carlo Erba 1106 analyzer. TLC: Merck precoated silica gel 60 F254 plates using UV light (254 nm) as a visualizing agent or 3% aq. $H_2PtCl_2$ – 10% aq. KI (1 : 1) or $KMnO_4$ ethanolic solution. Column chromatography: silica gel 60 ACC 35–70 μm Chromagel (SDS) or neutral alumina 90 activity II-III (Merck).

For the target compounds, the chemical purity was determined by HPLC using the following conditions. Waters Alliance 2690 and 2695 (software Millenium 3.20) and Agilent 1100 (software Chemstation A.06.03) equipment with XBridge C18 (3.5 μ, 0.46 × 10 cm column). Mobile phase: acetonitrile (ACN)/10 mM ammonium bicarbonate. Gradient conditions: 0–12 min: 5% ACN to 95% ACN; 12–17 min: isocratic 95% ACN. Flow rate: 1 mL min$^{-1}$. $T = 35$ °C; $\lambda = 210$ nm; $t_R = 5.4$ min.

### Materials

2-Methyl-3-phenylpropanoic acid **18** and 2-methylindan-1-one **19** are currently commercially available. 2-Methyl-1*H*-indene **24**[13] and 6-aminoindan-1-one **27**[14] were prepared as previously described and are currently commercially available. Diethyl methylmalonate, (2-chloroethyl)dimethylamine hydrochloride, 2-bromopyridine, 2-furaldehyde, 2-thiophenecarboxaldehyde, 3-fluorobenzaldehyde, 2-naphthalenesulfonyl chloride and 5-chloro-3-methyl-1-benzothiophene-2-sulfonyl chloride are commercial. 1-Methyl-1*H*-imidazole-2-carbaldehyde[15] was prepared as previously described.

### 2-Methylindan-1-one 19

To 2.6 g (11.30 mmol) of sodium in 50 mL of dry ethanol was added diethyl methylmalonate (20.0 g, 11.50 mmol) followed by addition of benzyl bromide (20.2 g, 11.80 mmol) under argon atmosphere. The resulting suspension was refluxed for 4 h. Water (60 mL) and potassium hydroxide (16.8 g, 29.0 mmol) were added and the mixture was refluxed for 4 h. After cooling to room temperature, the solvents were removed in vacuum and the residue was dissolved in 60 mL of water and acidified with concentrated HCl to pH = 1. The precipitate was filtered and dried to give the diacid, which was heated for decarboxylation for 2 h at 170 °C to yield 2-methyl-3-phenylpropanoic acid **18** (16.5 g, 88%) as a colorless oil. IR (thin film): ν(COO–H) 3028, ν(C=O) 1708 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.39 (d, $J$ = 7.2 Hz, 3H), 2.85–3.04 (m, 2H), 3.33 (dd, $J$ = 6.0, 12.0 Hz, 1H), 7.39–7.53 (m, 5H), 11.84 (br s, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 75.4 Hz): $\delta$ 16.9 ($CH_3$), 39.7 ($CH_2$), 41.7 (CH), 126.8 (CH), 128.8 (CH), 129.4 (CH), 139.4 (C), 183.2 (C=O) ppm. EI-MS *m/z*: 164 ($M^+$, 10%), 91 (100). Propanoic acid **18** (4.0 g, 24.51 mmol) was reacted at 100 °C for 1.5 h with thionyl chloride (5.35 mL, 73.53 mmol). The excess of thionyl chloride was removed in vacuum. The acid chloride was dissolved in dry toluene (15 mL) and added to a suspension of $AlCl_3$ (9.58 g, 73.53 mmol) in dry toluene (40 mL). The mixture was heated at reflux for 1.5 h and then cooled and poured into ice. After acidification with concentrated HCl to pH = 1, the mixture was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was distilled at 80–85 °C at 0.5 mmHg to give 2-methylindan-1-one **19** (2.64 g, 74%) as a yellow oil (lit.,[16] an oil).

IR (thin film): ν(C=O) 1710 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.32 (d, $J$ = 7.4 Hz, 3H), 2.68–2.80 (m, 2H), 3.38–3.49 (m, 1H), 7.36–7.47 (m, 2H), 7.57–7.63 (m, 1H), 7.76 (d, $J$ = 7.4 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 Hz): $\delta$ 16.3 ($CH_3$), 35.0 ($CH_2$), 42.0 (CH), 123.9 (CH), 126.5 (CH), 127.3 (CH), 134.6 (CH), 136.3 (C), 153.4 (C), 209.4 (C=O) ppm. EI-MS *m/z*: 146 ($M^+$, 70%), 131 (100).

### 2-Methyl-6-nitroindan-1-one 20 and 2-methyl-4-nitroindan-1-one 21

2-Methylindan-1-one **19** (20 g, 0.14 mol) was added in one portion to 95–97% $H_2SO_4$ (40 mL) at 0 °C. A solution of $KNO_3$ (15.2 g,

0.15 mol) in 95–97% $H_2SO_4$ (120 mL) was added dropwise. The mixture was stirred for 1 h at −5 °C and then poured over 2 L of ice. The mixture was stirred at room temperature for 18 h and extracted with $CH_2Cl_2$ (3 × 400 mL). The combined organic layers were washed with saturated $Na_2CO_3$ aqueous solution (400 mL) and water (2 × 400 mL), dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (hexanes–EtOAc mixtures of increasing polarity as eluent) to afford 2-methyl-6-nitroindan-1-one **20** (12 g, 46%), and 2-methyl-4-nitroindan-1-one **21** (2 g, 8%) as yellow solids.

**20.** Mp 70–72 °C. IR (thin film): ν(C=O) 1717; ν($NO_2$) 1529, 1348 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.37 (d, $J$ = 7.2 Hz, 3H), 2.84–2.88 (m, 2H), 3.51 (d, $J$ = 8.8 Hz, 1H), 3.55 (d, $J$ = 8.8 Hz, 1H), 7.64 (d, $J$ = 8.0 Hz, 1H), 8.45 (dd, $J$ = 2.4, 8.4 Hz, 1H), 8.56 (d, $J$ = 2.0 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 16.1 ($CH_3$), 35.1 ($CH_2$), 42.8 (CH), 119.3 (CH), 127.5 (CH), 128.8 (CH), 137.3, 147.8, 159.1, 206.9 (C=O) ppm. EI-MS $m/z$: 191 ($M^+$, 18%), 176 (36), 151 (100). Found: C 62.00, H 4.71, N 7.34. Calcd for $C_{10}H_9NO_3 \cdot 0.1H_2O$: C 62.24, H 4.80, N 7.26%.

**21.** Mp 74–76 °C. IR (KBr): ν(C=O) 1720; ν($NO_2$) 1523, 1353 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.38 (d, $J$ = 7.2 Hz, 3H); 2.78–2.86 (m, 1H); 3.21(dd, $J$ = 4.4, 20.0 Hz, 1H); 3.93 (dd, $J$ = 8.0, 16.0 Hz, 1H); 7.62 (dd, $J$ = 7.2, 8.0 Hz, 1H); 8.09 (d, $J$ = 7.2 Hz, 1H); 8.47 (dd, $J$ = 0.8, 8.0 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 16.1 ($CH_3$), 35.7 ($CH_2$), 41.6 (CH), 128.7 (CH), 129.8 (CH), 129.9 (CH), 134.0, 139.3, 148.1, 207.0 (C=O) ppm. EI-MS $m/z$: 191 ($M^+$, 98%), 151 (100). Found: C 61.07, H 4.84, N 7.15. Calcd for $C_{10}H_9NO_3 \cdot 0.33H_2O$: C 60.93, H 4.94, N 7.11%.

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

To a stirred solution of 2-methyl-6-nitroindan-1-one **20** (3.5 g, 18.31 mmol) in a 1 : 1 glacial acetic acid–water solution (70 mL) at 90 °C was added iron (8.2 g, 0.15 mol) in portions. The resulting suspension was stirred at the same temperature for 45 min. The reaction mixture was filtered through Celite® and evaporated. The resultant residue was dissolved in $CH_2Cl_2$ and washed with saturated $NaHCO_3$ aqueous solution (3 × 100 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness to afford 6-amino-2-methylindan-1-one **22** (2.5 g, 85%) as a yellow solid. The product was used directly in the next step without further purification.

Mp 144–146 °C. IR (KBr): ν($NH_2$) 3461, 3358; ν(C=O) 1688 $cm^{-1}$. $^1H$ NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.14 (d, $J$ = 7.4 Hz, 3H), 2.40–2.60 (m, 2H), 3.10–3.25 (m, 1H), 5.28 (br s, 2H), 6.75 (d, $J$ = 1.8 Hz, 1H), 6.91 (dd, $J$ = 2.6, 10.0 Hz, 1H), 7.18 (d, $J$ = 8.0 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 16.3 ($CH_3$), 33.7 ($CH_2$), 42.0 (CH), 105.7 (CH), 122.4 (CH), 126.8 (CH), 136.7, 141.1, 148.4, 208.8 (C=O) ppm. EI-MS $m/z$: 161 ($M^+$, 99%), 146 (100), 132 (51). Found: C 67.68, H 6.71, N 7.90. Calcd for $C_{10}H_{11}NO \cdot 0.25CH_2Cl_2$: C 67.48, H 6.35, N 7.68%.

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

10% Pd/C (0.3 g) was added to a solution of 2-methyl-4-nitroindan-1-one **21** (3.0 g, 15.7 mmol) in absolute ethanol (250 mL) and the mixture was hydrogenated under atmospheric pressure. After 18 h, the catalyst was filtered and the filtrate was concentrated in vacuum. The residue was taken up in 1 N HCl (50 mL) and washed with EtOAc (3 × 50 mL). The aqueous phase was basified with 10% NaOH aqueous solution (80 mL). The resulting solid was filtered and dried to give 4-amino-2-methylindan-1-one **23** (1.01 g, 40%) as a yellow oil.

IR (thin film): ν($NH_2$) 3367; ν(C=O) 1694 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.33 (d, $J$ = 7.4 Hz, 3H), 2.47 (dd, $J$ = 3.6, 16.6 Hz, 1H), 2.67–2.80 (m, 1H), 3.17 (dd, $J$ = 7.6, 16.5 Hz, 1H), 3.78 (br s, 2H), 6.86–6.90 (m, 1H), 7.20–7.26 (m, 2H) ppm. $^{13}C$ NMR ($CDCl_3$, 100.6 Hz): $\delta$ 16.5 ($CH_3$), 31.6 ($CH_2$), 41.8 (CH), 113.8 (CH), 119.1 (CH), 128.7 (CH), 137.1, 138.5, 143.7, 209.6 (C=O) ppm. ESI-HRMS calcd for $C_{10}H_{12}NO$ $[M + H]^+$ 162.0919; found 162.0913.

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

To a stirred solution of 2-methyl-1*H*-indene **24** (0.75 g, 5.77 mmol) in dry THF (15 mL) cooled to −5 °C was added *n*-BuLi (1.6 M in hexanes, 3.6 mL, 5.77 mmol) under argon atmosphere. After stirring for 3 h at room temperature, (2-chloroethyl)dimethylamine hydrochloride (0.42 g, 2.88 mmol) was added as a solid. The solution was allowed to stir overnight and was hydrolyzed with water (25 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated to dryness. The resulting residue was purified by column chromatography on alumina (hexanes–EtOAc mixtures of increasing polarity as eluent) to afford the amine derivative **25** (0.36 mg, 60%) as an oil (lit.,[17] colorless oil).

$^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.08 (s, 3H), 2.36 (s, 6H), 2.40–2.50 (m, 2H), 2.63–2.80 (m, 2H), 3.27 (s, 2H), 7.01–7.40 (m, 4H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 14.0 ($CH_3$), 23.8 ($CH_2$), 42.6 ($CH_2$), 45.3 ($CH_3$), 58.3 ($CH_2$), 117.9 (CH), 123.2 (CH), 123.6 (CH), 126.0 (CH), 134.6, 139.4, 142.5, 146.3 ppm. EI-MS $m/z$: 201 ($M^+$, 2%), 58 (100).

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

To a stirred solution of 2-bromopyridine (1.3 mL, 13.68 mmol) in dry diethyl ether (10 mL) cooled to −60 °C was added *n*-BuLi (1.6 M in hexanes, 9.0 mL, 13.68 mmol) under argon atmosphere. The resulting mixture reaction was stirred for 20 min at this temperature. Thereafter, a solution of 2-methylindan-2-one **19** (2.0 g, 13.68 mmol) in dry ethyl ether (12 mL) was added. After a reaction time of 2 h at −50 °C, the reaction was hydrolyzed with saturated aqueous $NH_4Cl$ solution (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated to dryness to afford a brown oil. The obtained compound was treated at 0 °C with 96% $H_2SO_4$. The solution was stirred for 2 h at this temperature and then poured into ice (200 g). The resulting reaction mixture was neutralized with solid NaOH and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated to dryness. The resulting residue was purified by column chromatography on silica (hexanes–EtOAc mixtures of increasing polarity as eluent) to give the pyridine derivative **26** as a yellow oil, yield 10%.

$^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.25 (s, 3H), 3.50 (s, 2H), 7.10–7.28 (m, 4H), 7.42–7.46 (m, 2H), 7.74–7.82 (m, 1H), 8.74–8.76

(m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 Hz): $\delta$ 15.2 ($CH_3$), 43.6 ($CH_2$), 119.7 (CH), 121.6 (CH), 123.2 (CH), 124.0 (CH), 124.1 (CH), 126.1 (CH), 132.2, 136.1 (CH), 142.1, 143.8, 145.2, 149.6 (CH), 154.8 ppm.

### Synthesis of (*Z*)-heteroarylmethylideneindenes 8–11: General procedure

To a stirred solution of amine **25** or **26** (1 equiv) in dry MeOH at −5 °C was added sodium (2.5 equiv) in dry MeOH under argon atmosphere. The mixture was warmed to room temperature and stirred for 20 min. To this mixture was added the corresponding aldehyde (1.05 equiv) and the reaction mixture was heated at reflux for 12 h. After dilution with EtOH, the solvent was removed in vacuum. The indene derivatives **8–11** were isolated from the crude reaction mixture by column chromatography on alumina using hexanes–EtOAc mixtures of increasing polarity as the eluent.

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

The above procedure was followed using amine **25** (170 mg, 0.84 mmol) in dry MeOH (5 mL), sodium (50 mg, 2.1 mmol) in dry MeOH (5 mL) and 2-furaldehyde (0.08 mL, 0.88 mmol). To a solution of the resultant crude product in dry acetone (1 mL) was added HCl (2.0 M in diethyl ether, 1 mL). The yellow solid obtained was filtered and dried to afford the hydrochloride **8**·HCl, yield 30%.

Mp 170–171 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.20 (s, 3H), 2.90 (s, 6H), 3.12–3.19 (m, 4H), 6.67 (s, 1H), 6.92 (s, 1H), 7.00–7.08 (m, 1H), 7.20–7.32 (m, 2H), 7.52 (s, 1H), 7.68 (s, 1H), 7.81 (d, $J$ = 8.0 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 Hz): $\delta$ 10.5 ($CH_3$), 21.1 ($CH_2$), 42.9 ($CH_3$), 56.3 ($CH_2$), 111.5 (CH), 117.5 (CH), 120.5 (CH), 121.4, 122.9 (CH), 124.9 (CH), 128.0 (CH), 132.1, 134.1, 136.1, 141.0, 142.8 (CH), 143.3 (CH) ppm. ESI-HRMS calcd for $C_{19}H_{22}NO$ $[M + H]^+$ 280.1696; found 280.1692.

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

The above procedure was followed using amine **25** (368 mg, 1.83 mmol) in dry MeOH (10 mL), sodium (105 mg, 4.58 mmol) in dry MeOH (10 mL) and 2-thiophenecarboxaldehyde (0.18 mL, 1.92 mmol). Compound **9** was obtained as an orange oil, yield 28%.

$^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.13 (s, 3H), 2.34 (s, 6H), 2.42–2.52 (m, 2H), 2.72–2.82 (m, 2H), 6.89–7.01 (m, 1H), 7.05 (s, 1H), 7.06–7.12 (m, 1H), 7.17–7.20 (m, 2H), 7.34–7.43 (m, 2H), 7.87 (d, $J$ = 8 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 Hz): $\delta$ 10.3 ($CH_3$), 24.1 ($CH_2$), 45.3 ($CH_3$), 58.1 ($CH_2$), 117.7 (CH), 120.7 (CH), 122.7 (CH), 124.4 (CH), 127.2 (CH), 127.4 (CH), 127.9 (CH), 129.2 (CH), 134.0, 134.1, 137.4, 139.2, 141.8, 144.2 ppm. ESI-HRMS calcd for $C_{19}H_{22}NS$ $[M + H]^+$ 296.1468; found 296.1467.

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

The above procedure was followed using amine **25** (430 mg, 2.14 mmol) in dry MeOH (12 mL), sodium (123 mg, 5.35 mmol) in dry MeOH (12 mL) and 1-methyl-1*H*-imidazole-2-carbaldehyde (247 mg, 2.25 mmol). Compound **10** was obtained as an orange oil, yield 29%.

$^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.12 (s, 3H), 2.33 (s, 6H), 2.40–2.52 (m, 2H), 2.68–2.80 (m, 2H), 3.66 (s, 3H), 6.65 (s, 1H), 6.94 (s, 1H), 7.01–7.19 (m, 3H), 7.25 (s, 1H), 8.51 (d, $J$ = 8 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 Hz): $\delta$ 10.2 ($CH_3$), 24.3 ($CH_2$), 33.4 ($CH_3$), 45.4 ($CH_3$), 58.1 ($CH_2$), 112.2 (CH), 117.4 (CH), 121.8 (CH), 125.0 (CH), 125.3 (CH), 128.2 (CH), 129.2 (CH), 133.4, 134.1, 138.9, 144.2 ppm. ESI-HRMS calcd for $C_{19}H_{24}N_3$ $[M + H]^+$ 294.1965; found 294.1960.

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

The above procedure was followed using amine **26** (270 mg, 1.30 mmol) in dry MeOH (10 mL), sodium (75 mg, 3.25 mmol) in dry MeOH (10 mL) and 2-thiophenecarboxaldehyde (0.13 mL, 1.37 mmol). To a solution of the resultant crude product in dry MeOH (2 mL) was added HCl (2.0 M in diethyl ether, 5 mL) and $CH_2Cl_2$ (2 mL). The red solid obtained was filtered and dried to afford the hydrochloride **11**·HCl (45 mg, 10%).

Mp 203–205 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.54 (s, 3H), 7.13–7.22 (m, 3H), 7.55–7.60 (m, 3H), 7.86 (dd, $J$ = 6.2 and 6.4 Hz, 1H), 8.00 (d, $J$ = 8 Hz, 1H), 8.23 (d, $J$ = 7.8 Hz, 1H), 8.46 (dd, $J$ = 7.6 and 7.5 Hz, 1H), 9.08 (d, $J$ = 8 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 Hz): $\delta$ 14.5 ($CH_3$), 123.3 (CH), 125.9 (CH), 127.7 (CH), 128.0 (CH), 128.7 (CH), 129.6 (CH), 131.8 (CH), 133.5 (CH), 138.2, 139.6, 141.1, 143.6, 144.9, 147.3, 149.9 ppm. ESI-HRMS calcd for $C_{20}H_{16}NS$ $[M + H]^+$ 302.1000; found 302.0995.

### Synthesis of indanones sulfonamides 28–31: General procedure

To a stirred solution of aminoindanones **22**, **23** or **27** (1 equiv) and pyridine in dry $CH_2Cl_2$ was added a solution of a convenient substituted aromatic sulfonyl chloride (1.3 equiv) in dry $CH_2Cl_2$ under argon atmosphere. After stirring at room temperature for 18 h, the reaction mixture was washed with 2.5 N HCl, dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness.

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

The above procedure was followed using aminoindanone **22** (2.5 g, 15.51 mmol), dry pyridine (3 mL) in dry $CH_2Cl_2$ (65 mL) and 2-naphthalenesulfonyl chloride (3.5 g, 20.16 mmol) in dry $CH_2Cl_2$ (20 mL). Indanone sulfonamide **28** (3.7 g, 68%) was obtained as an off-white solid. The product was used directly in the next step without further purification.

Mp 174–176 °C. IR (KBr): ν(NH) 3177; ν(C=O) 1693; ν($SO_2$) 1341, 1158 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.24 (d, $J$ = 7.2 Hz, 3H), 2.50–2.80 (m, 2H), 3.20–3.39 (m, 1H), 7.31 (d, $J$ = 10.0 Hz, 1H), 7.43–7.44 (m, 1H), 7.49–7.62 (m, 4H), 7.79–7.90 (m, 4H), 8.39 (s, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 Hz): $\delta$ 16.1 ($CH_3$), 34.4 ($CH_2$), 42.5 (CH), 116.0 (CH), 122.0 (CH), 127.4 (CH), 127.5 (CH), 127.8 (CH), 128.3 (CH), 128.8 (CH), 128.9 (CH), 129.2 (CH), 129.5 (CH), 131.9, 134.8, 135.6, 136.2, 137.2, 150.2, 208.7 (C=O) ppm. EI-MS *m*/*z*: 351 ($M^+$, 40%), 127 (100). Found: C 67.58, H 5.12, N 3.95. Calcd for $C_{20}H_{17}NO_3S$·0.33EtOH: C 67.68, H 5.22, N 3.82%.

### *N*-(3-Oxo-2,3-dihydro-1*H*-inden-5-yl)naphthalene-2-sulfonamide 29

The above procedure was followed using aminoindanone **27** (3.0 g, 20.40 mmol), dry pyridine (4 mL) in dry $CH_2Cl_2$ (100 mL) and 2-naphthalenesulfonyl chloride (6.0 g, 26.49 mmol) in dry $CH_2Cl_2$ (25 mL). The resulting residue was purified by column chromatography on silica ($CH_2Cl_2$–MeOH mixtures of increasing polarity as eluent) to give indanone sulfonamide **29** (3.55 g, 53%) as an off-white solid.

Mp 211–212 °C. IR (KBr): ν(NH) 3200; ν(C=O) 1693; ν($SO_2$) 1334, 1154 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.60–2.67 (m, 2H), 3.01–3.05 (m, 2H), 6.93 (s, 1H), 7.35–7.39 (m, 2H), 7.45–7.78 (m, 4H), 7.82–7.92 (m, 4H), 8.39 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 25.5 ($CH_2$), 36.8 ($CH_2$), 116.1 (CH), 122.1 (CH), 127.8 (CH), 128.0 (CH), 128.6 (CH), 129.1 (CH), 129.2 (CH), 129.4 (CH), 129.7 (CH), 132.1, 135.1, 135.7, 136.1, 138.1, 152.2, 206.1 (C=O) ppm. EI-MS *m*/*z*: 337 ($M^+$, 26%), 146 (100). Found: C 65.09, H 4.47, N 4.02. Calcd for $C_{19}H_{15}NO_3S{\cdot}0.7H_2O$: C 65.20, H 4.72, N 4.00%.

### 5-Chloro-3-methyl-*N*-(2-methyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl)-1-benzothiophene-2-sulfonamide 30

The above procedure was followed using aminoindanone **22** (1.0 g, 6.20 mmol) in dry pyiridine (40 mL) and 5-chloro-3-methyl-1-benzothiophene-2-sulfonyl chloride (1.83 g, 6.51 mmol) in dry pyridine (9 mL). The resulting residue was purified by column chromatography on silica ($CH_2Cl_2$–MeOH mixtures of increasing polarity as eluent) to give indanone sulfonamide **30** (1.2 g, 48%) as a salmon-pink solid.

Mp 245–246 °C. IR (KBr): ν(NH) 3120; ν(C=O) 1691; ν($SO_2$) 1342, 1158 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.28 (d, $J$ = 7.2 Hz, 3H), 2.62–2.90 (m, 6H), 3.36–3.52 (m, 4H), 7.54 (s, 1H), 7.59 (s, 2H), 7.72 (d, $J$ = 8.0 Hz, 1H), 8.18 (s, 1H), 8.39 (s, $J$ = 8.0 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 Hz): $\delta$ 12.5 ($CH_3$), 16.1 ($CH_3$), 34.3 ($CH_2$), 42.4 (CH), 114.2 (CH), 124.0 (CH), 125.2 (CH), 127.7 (CH), 128.2 (CH), 128.3 (CH), 131.1, 136.9, 137.0, 137.1, 137.6, 140.9, 150.1, 208.5 (C=O) ppm. EI-MS *m*/*z*: 405 ($M^+$, 9%), 146 (91), 181 (100). Found: C 55.13, H 3.90, N 3.53, S 14.95. Calcd for $C_{20}H_{17}NO_3S{\cdot}0.15CH_2Cl_2$: C 54.94, H 3.92, N 3.35, S 15.32%.

### *N*-(2-Methyl-3-oxo-2,3-dihydro-1*H*-inden-7-yl)naphthalene-2-sulfonamide 31

The above procedure was followed using aminoindanone **23** (0.72 g, 4.47 mmol), dry pyridine (1.5 mL) in dry $CH_2Cl_2$ (30 mL) and 2-naphthalenesulfonyl chloride (1.3 g, 5.81 mmol) in dry $CH_2Cl_2$ (10 mL). Indanone sulfonamide **31** (1.35 g, 83%) was obtained as an off-white foamy solid. The product was used directly in the next step without further purification.

Mp 85–86 °C. IR (KBr): ν(NH) 3241; ν(C=O) 1697; ν($SO_2$) 1338, 1159 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.06 (d, $J$ = 7.2 Hz, 3H), 2.19–2.29 (m, 1H), 2.42–2.62 (m, 1H), 3.00–3.13 (m, 1H), 6.78 (s, 1H), 7.29 (m, 1H), 7.54–7.95 (m, 8H), 8.33 (d, $J$ = 1.8 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 16.1 ($CH_3$), 32.0 ($CH_2$), 41.7 (CH), 121.4 (CH), 121.9 (CH), 127.8 (CH), 127.9 (CH), 128.4 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 129.2 (CH), 129.6 (CH), 131.8, 134.1, 134.9, 135.9, 137.5, 146.2, 208.4 (C=O) ppm. ESI-HRMS calcd for $[M + H]^+$ 352.1001; found 352.0997.

### Ethyl (2*Z*)-{2-methyl-6-[(2-naphthylsulfonyl)amino]-2,3-dihydro-1*H*-inden-1-ylidene}acetate 32

To a stirred suspension of 55–65% NaH (0.95 g, 39.04 mmol) in dry THF (200 mL) cooled to 0 °C was added dropwise triethyl phosphonoacetate (6.9 mL, 34.10 mmol) under argon atmosphere. After stirring for 1 h at the same temperature, a solution of indanone sulfonamide **28** (1.2 g, 3.41 mmol) in dry THF (35 mL) was slowly added. The resultant yellow solution was stirred at room temperature for 1.5 h and at reflux for 24 h. The reaction mixture was quenched by addition of water (150 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (hexanes–EtOAc mixtures of increasing polarity as eluent) to afford the ethyl (*Z*)-indanylacetate **32** (1.06 g, 73%) as a yellow solid.

Mp 118–120 °C. IR (KBr): ν(NH) 3183; ν(C=O) 1682; ν(C=C) 1628; ν($SO_2$) 1332, 1160 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.17–1.30 (m, 9H), 2.45–2.55 (m, 1H), 2.98–3.15 (m, 2H), 4.11 (q, $J$ = 6.8 Hz, 2H), 5.78 (d, $J$ = 1.4 Hz, 1H), 6.61 (s, 1H), 7.16 (d, $J$ = 8.6 Hz, 1H), 7.26–7.34 (m, 1H), 7.54–7.62 (m, 2H), 7.74–7.96 (m, 4H), 8.40 (d, $J$ = 2.2 Hz, 1H), 8.45 (d, $J$ = 1.8 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 14.3 ($CH_3$), 20.9 ($CH_3$), 38.0 ($CH_2$), 41.8 (CH), 60.0 ($CH_2$), 111.7 (CH), 121.5 (CH), 122.4 (CH), 124.1 (CH), 125.5 (CH), 127.2 (CH), 127.7 (CH), 128.6 (CH), 129.0 (CH), 129.2 (CH), 129.3 (CH), 131.8, 135.2, 136.0, 137.8, 145.7, 163.8, 166.2 (C=O) ppm. EI-MS *m*/*z*: 421 ($M^+$, 64%), 375 (94), 184 (100). Found: C 64.70, H 5.59, N 3.18. Calcd for $C_{24}H_{23}NO_4S{\cdot}0.4CH_2Cl_2$: C 64.34, H 5.27, N 3.08%.

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

To a stirred suspension of ester derivative **32** (2.15 g, 5.10 mmol) in dry MeOH (25 mL) at room temperature was slowly added sodium (0.47 g, 20.40 mmol) in dry MeOH (25 mL) under argon atmosphere. The resulting solution was refluxed for 18 h. The reaction mixture was quenched by addition of water (150 mL) and acidified with 5 N HCl. The resultant solid was filtered to give acetic acid derivative **33** (1.89 g, 94%) as a light orange solid.

Mp 176–178 °C. IR (KBr): ν(COO–H, NH) 3242; ν(C=O) 1705; ν($SO_2$) 1329, 1155 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.07 (s, 3H), 3.20 (s, 2H), 3.48 (s, 2H), 6.85–6.95 (m, 1H), 7.08–7.18 (m, 2H), 7.40–7.95 (m, 7H), 8.31 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 14.2 ($CH_3$), 31.2 ($CH_2$), 42.2 ($CH_2$), 112.4 (CH), 117.3 (CH), 122.2 (CH), 123.5 (CH), 127.2 (CH), 127.7 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 131.8, 134.7, 134.9, 135.8, 139.0, 144.2, 146.7, 175.3 (C=O) ppm. EI-MS *m*/*z*: 393 ($M^+$, 36%), 202 (100). Found: C 66.03, H 5.10, N 3.39, S 7.04. Calcd for $C_{22}H_{19}NO_4S{\cdot}0.5EtOAc$: C 65.89, H 5.30, N 3.20, S 7.33%.

### Synthesis of ethyl acetates 34a and 34b

To a stirred suspension of 55–65% NaH (0.82 g, 34.19 mmol) in dry DME (75 mL) cooled to 0 °C was added dropwise triethyl phosphonoacetate (5.9 mL, 29.60 mmol) under argon atmosphere.

After stirring for 1 h at the same temperature, a solution of indanone **29** (1.0 g, 2.96 mmol) in dry DME (25 mL) was slowly added. The resultant solution was stirred at reflux for 24 h. The reaction mixture was quenched by addition of water and extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (hexanes–EtOAc mixtures of increasing polarity as eluent). The mixture of isomeric esters **34a** and **34b** (230 mg, 19%) was obtained as a yellow solid.

EI-MS *m/z* (%): 407 ($M^+$, 60), 361 (56), 216 (54), 188 (60), 170 (85), 127 (100), 115 (90).

### *N*-Ethyl-*N*-(3-oxo-2,3-dihydro-1*H*-inden-5-yl)naphthalene-2-sulfonamide 35

**Experiment 1.** To a solution of anhydrous LiBr (6.18 g, 71.16 mmol) in dry DME was added triethyl phosphonoacetate (11.9 mL, 59.30 mmol) and the mixture was stirred 5 min under argon atmosphere. Dry triethylamine (9.5 mL, 68.49 mmol) was added and the white suspension stirred for an additional 10 min. A solution of indanone **29** (2.0 g, 5.93 mmol) in dry DME (60 mL) was then added dropwise, and the reaction mixture was stirred at reflux for 24 h. After being quenched with 1 N HCl, the reaction mixture was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (hexanes–EtOAc mixtures of increasing polarity as eluent). *N*-Ethyl-*N*-indan-1-one sulfonamide **35** (680 mg, 31%) was obtained as an off-white solid.

**Experiment 2.** To a solution of indanone sulfonamide **29** (1.0 g, 2.96 mmol) in dry THF (100 mL) was added triethyl phosphonoacetate (5.9 mL, 29.60 mmol) and activated 4 Å molecular sieves (5 g) under argon atmosphere, and the mixture heated at reflux. $LiOH{\cdot}H_2O$ (1.43 g, 34.19 mmol) previously submitted to heating at 120 °C for 2 h was added, in three portions, during the course of the reaction (24 h). After being quenched with 1 N HCl, the reaction mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (hexanes–EtOAc mixtures of increasing polarity as eluent). *N*-Ethyl-*N*-indan-1-one sulfonamide **35** (100 mg, 9%) was obtained as an off-white solid.

Mp 111–112 °C. IR (KBr): ν(C=O) 1700; ν($SO_2$) 1342, 1162 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.07 (t, $J = 7.2$ Hz, 3H), 2.70–2.74 (m, 2H), 3.14–3.18 (m, 2H), 3.66 (q, $J = 7.2$ Hz, 2H), 7.30 (s, 1H), 7.49–7.68 (m, 5H), 7.87–7.91 (m, 3H), 8.22 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 Hz): $\delta$ 13.9 ($CH_3$), 25.6 ($CH_2$), 36.6 ($CH_2$), 45.6 ($CH_2$), 122.6 (CH), 122.7 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 127.9 (CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 132.0, 134.8, 135.0, 136.3 (CH), 137.8, 138.4, 154.6, 205.9 (C=O) ppm. EI-MS *m/z*: 393 ($M^+$, 16%), 127 (100).

### Synthesis of (3-indenyl)acetic acids 36–38: General procedure

Dry ethyl acetate (1.05 equiv) was added dropwise to a stirred solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 2.1 equiv) at −78 °C. After 15 min, a solution of indanone sulfonamides **29**, **30** or **31** (1 equiv) in dry THF was added dropwise and the mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched by addition of 1 N HCl and was warmed to ambient temperature. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were evaporated to dryness. Trifluoroacetic acid (7 equiv) was added dropwise to a stirred solution of the resulting residue in dry $CH_2Cl_2$ at −5 °C. After 35 min, the mixture was concentrated in vacuum. To a stirred solution of the resultant foamy solid in dry MeOH at room temperature was added sodium (4 equiv) in dry MeOH under argon atmosphere. The resulting mixture was refluxed for 24 h. To cooled reaction mixture EtOH was added dropwise, and the mixture then evaporated. To the residue was added 5% aqueous $Na_2CO_3$solution and washed with EtOAc. The aqueous layer was acidified with 5 N HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness.

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

The above procedure was followed using dry EtOAc (0.47 mL, 4.67 mmol), LHMDS (1.0 M in THF, 9.3 mL, 9.3 mmol), indanone sulfonamide **29** (1.5 g, 4.45 mmol) in dry THF (35 mL); TFA (2.1 mL, 27.66 mmol) in dry $CH_2Cl_2$ (20 mL) and sodium (0.4 g, 17.28 mmol) in dry MeOH (40 mL). (3-Indenyl)acetic acid **36** (0.95 g, 56%) was obtained as a foamy yellow solid.

Mp 135–136 °C. IR (KBr): ν(COO–H, NH) 3276; ν(C=O) 1702; ν($SO_2$) 1325, 1156 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 3.15 (s, 2H), 3.49 (s, 2H), 6.37 (s, 1H), 6.90–7.96 (m, 10H), 8.32 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 33.7 ($CH_2$), 37.5 ($CH_2$), 113.3 (CH), 118.6 (CH), 122.2 (CH), 124.1 (CH), 127.2 (CH), 127.6 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 131.8, 133.8 (CH), 134.7, 134.9, 135.7, 141.0, 145.3, 175.8 (C=O) ppm. EI-MS *m/z*: 379 ($M^+$, 11%), 127 (100).

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

The above procedure was followed using dry EtOAc (0.23 mL, 2.33 mmol), LHMDS (1.0 M in THF, 4.7 mL, 4.7 mmol), indanone sulfonamide **30** (0.9 g, 2.22 mmol) in dry THF (22 mL); TFA (1.1 mL, 14.41 mmol) in dry $CH_2Cl_2$ (15 mL) and sodium (0.22 g, 9.61 mmol) in dry MeOH (25 mL). (3-Indenyl)acetic acid **37** (0.58 g, 54%) was obtained as a foamy white solid.

Mp 197–198 °C. IR (KBr): ν(COO–H, NH) 3266; ν(C=O) 1710; ν($SO_2$) 1342, 1155 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.10 (s, 2H), 2.32 (s, 3H), 3.28 (s, 2H), 3.48 (s, 2H), 6.86–6.95 (m, 1H), 7.02–7.06 (m, 2H), 7.19–7.33 (m, 2H), 7.58–7.61 (m, 2H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 12.6 ($CH_3$), 14.6 ($CH_3$), 31.8 ($CH_2$), 42.1 ($CH_2$), 112.2 (CH), 117.2 (CH), 124.0 (CH), 125.2 (CH), 128.0 (CH), 130.2, 131.2, 135.8, 137.2, 137.8, 138.1, 139.0, 140.8, 144.0, 147.8, 172.3 (C=O) ppm. EI-MS *m/z*: 447 ($M^+$, 13%), 202 (89), 156 (100).

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

The above procedure was followed using dry EtOAc (0.17 mL, 1.79 mmol), LHMDS (1.0 M in THF, 3.6 mL, 3.6 mmol), indanone sulfonamide **31** (0.6 g, 1.71 mmol) in dry THF (12 mL); TFA

(0.7 mL, 8.76 mmol) in dry $CH_2Cl_2$ (9 mL) and sodium (0.11 g, 4.74 mmol) in dry MeOH (11 mL). (3-Indenyl)acetic acid **38** (0.46 g, 68%) was obtained as a foamy light brown solid.

Mp 91–92 °C. IR (KBr): ν(COO–H, NH) 3251; ν(C=O) 1703; ν($SO_2$) 1328, 1158 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.04 (s, 3H), 3.15 (s, 2H), 3.45 (s, 2H), 6.82–7.80 (m, 10H), 8.31 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 14.2 ($CH_3$), 31.5 ($CH_2$), 42.1 ($CH_2$), 112.4 (CH), 117.5 (CH), 122.2 (CH), 123.5 (CH), 127.2 (CH), 127.6 (CH), 128.5 (CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 131.8, 134.6, 134.9, 135.8, 139.0, 144.2, 147.4, 176.0 (C=O) ppm. EI-MS *m/z*: 393 ($M^+$, 21%), 202 (59), 156 (100), 127 (91). Found: C 65.51, H 5.21, N 3.40, S 7.06. Calcd for $C_{22}H_{19}NO_4S{\cdot}0.5$EtOAc: C 65.89, H 5.30, N 3.20, S 7.33%.

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

To a stirred suspension of 55–65% NaH (0.55 g, 22.86 mmol) in dry THF (75 mL) cooled to 0 °C was added dropwise a solution of (3-indenyl)acetic acid **33** (1.5 g, 3.81 mmol) in dry THF (40 mL). After stirring at room temperature for 1 h, a solution of benzaldehyde (2 mL, 19.05 mmol) in dry THF (10 mL) was slowly added. The resulting mixture was heated to reflux for 5 h. The reaction mixture was quenched with ethanol (50 mL) and evaporated. The resultant residue was dissolved in brine (200 mL) and washed with $CH_2Cl_2$ (2 × 150 mL). The aqueous layer was acidified with 5 N HCl and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (hexanes–EtOAc mixtures of increasing polarity as eluent) to afford the acetic acid derivative (*Z*)-**39** (0.7 g, 38%) as a yellow solid.

Mp 110–112 °C. IR (KBr): ν(COO–H, NH) 3245; ν(C=O) 1705; ν(C=C) 1607; ν($SO_2$) 1330, 1154 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.18 (s, 3H), 3.58 (s, 2H), 7.00 (s, 1H), 7.14–7.17 (m, 2H), 7.33–7.80 (m, 12H), 8.32 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 10.5 ($CH_3$), 30.9 ($CH_2$), 111.2 (CH), 116.2 (CH), 122.1 (CH), 123.2 (CH), 126.6 (CH), 128.0 (CH), 128.3 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 130.7, 131.8, 135.4, 135.8, 136.3, 136.4, 138.0, 140.3, 145.2, 175.4 (C=O) ppm. EI-MS *m/z*: 481 ($M^+$, 2%), 202 (100).

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

To a stirred solution of the acetic acid derivative **39** (0.2 g, 0.42 mmol) in dry THF (30 mL) was added in portions 1,1′-carbonyldiimidazole (140 mg, 0.84 mmol) under an argon atmosphere. The resulting mixture was stirred at room temperature for 2 h., and then dimethylamine (2 M in THF, 0.42 mL, 0.84 mmol) was added. After stirring for 18 h, the reaction mixture was evaporated, dissolved in EtOAc (100 mL) and washed with water (3 × 50 mL). The organic layer was dried with anhydrous $Na_2SO_4$, filtered and evaporated to dryness to give the acetamide derivative **40** (0.16 g, 75%) as a yellow oil. The product was used directly in the next step without further purification.

IR (thin film): ν(NH) 3247; ν(C=O) 1606; ν($SO_2$) 1334, 1159 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.14–2.18 (m, 3H), 2.85–2.98 (m, 6H), 3.49–3.57 (m, 2H), 6.61–6.73 (m, 1H), 7.04–7.83 (m, 14H), 8.32–8.36 (m, 1H) ppm. EI-MS *m/z*: 508 ($M^+$, 17%), 72 (100).

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

To a stirred suspension of $LiAlH_4$ (35 mg, 0.88 mmol) in dry THF (20 mL) was added dropwise a solution of acetamide derivative **40** (110 mg, 0.22 mmol) in dry THF (10 mL). The resulting mixture was heated at reflux for 2 h. The reaction mixture was quenched by addition of water (20 mL) and 10% $H_2SO_4$ aqueous solution (20 mL), stirred for 30 min and extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel ($CH_2Cl_2$–MeOH–$NH_4OH$ mixtures of increasing polarity as eluent) to afford the indene derivative (*Z*)-**12** (10 mg, 9%) as a yellow foamy solid. Chemical purity by HPLC: 83.1%.

$^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.10 (s, 3H), 2.28 (s, 6H), 2.28–2.40 (m, 2H), 2.60–2.72 (m, 2H), 6.58–6.64 (m, 1H), 6.88–6.92 (m, 1H), 7.09–7.17 (m, 2H), 7.32–7.86 (m, 13H), 8.38 (s, 1H) ppm.

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

To a stirred solution of the (3-indenyl)acetic acid **33** (0.4 g, 1.02 mmol) in dry THF (50 mL) was added in portions 1,1′-carbonyldiimidazole (140 mg, 0.84 mmol) under argon atmosphere. The resulting mixture was stirred at room temperature for 2 h and then dimethylamine (2M in THF, 1.02 mL, 2.04 mmol) was added. After stirring for 18 h, the reaction mixture was evaporated, dissolved in EtOAc (100 mL) and washed with water (3 × 50 mL). The organic layer was dried with anhydrous $Na_2SO_4$, filtered and evaporated to dryness to give the acetamide derivative **41** (0.3 g, 71%) as a yellow solid. The product was used directly in the next step without further purification.

Mp 114–116 °C. IR (thin film): ν(NH) 3250; ν(C=O) 1610; ν($SO_2$) 1333, 1159 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.05 (s, 3H), 2.86 (s, 3H), 2.96 (s, 3H), 3.23 (s, 2H), 3.45 (s, 2H), 6.78–7.18 (m, 4H), 7.54–7.94 (m, 5H), 8.38 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 14.3 ($CH_3$), 31.6 ($CH_2$), 35.8 ($CH_3$), 37.5 ($CH_3$), 42.3 ($CH_2$), 113.0 (CH), 117.8 (CH), 122.5 (CH), 123.3 (CH), 127.1 (CH), 127.7 (CH), 128.5 (CH), 128.6 (CH), 129.0 (CH), 129.2 (CH), 131.9, 134.6, 134.9, 136.2, 139.2, 142.5, 147.0, 170.4 (C=O) ppm. EI-MS *m/z*: 420 ($M^+$, 15%), 72 (100).

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

To a stirred solution of $AlH_3$–$NMe_2Et$ (0.5 M in toluene, 1.4 mL, 0.68 mmol) in dry THF (10 mL) cooled to 0 °C was added *via* a hypodermic syringe a solution of acetamide derivative **41** (70 mg, 0.17 mmol) in dry THF (10 mL) previously cooled to 0 °C, under argon atmosphere. After stirring at 0 °C for 30 min, the reaction mixture was hydrolyzed with water (5 mL) and 10% $H_2SO_4$ aqueous solution (5 mL), stirred at room temperature and basified with 20% aqueous ammonia. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue

was purified by column chromatography on silica gel ($CH_2Cl_2$–MeOH–$NH_3$ mixtures of increasing polarity as eluent) to afford the indene derivative **13** (32 mg, 46%) as a yellow oil.

IR (thin film): ν(NH) 3252; ν($SO_2$) 1329, 1158 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.99 (s, 3H), 2.23 (s, 6H), 2.23–2.30 (m, 2H), 2.48–2.59 (m, 2H), 3.15 (s, 2H), 6.90–6.93 (m, 2H), 7.14–7.18 (m, 1H), 7.48–7.60 (m, 2H), 7.76–7.86 (m, 4H), 8.35 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 14.0 ($CH_3$), 23.4 ($CH_2$), 42.1 ($CH_2$), 45.1 ($CH_3$), 57.8 ($CH_2$), 112.8 (CH), 118.3 (CH), 122.5 (CH), 123.5 (CH), 127.2 (CH), 127.7 (CH), 128.6 (CH), 128.7 (CH), 129.0 (CH), 129.2 (CH), 132.0, 134.0, 134.8, 135.0, 136.1, 139.8, 141.4, 147.6 ppm. Found: C 60.12, H 5.32, N 5.26. Calcd for $C_{24}H_{26}N_2O_2S{\cdot}1.1CH_2Cl_2$: C 60.30, H 5.68, N 5.60%.

### Synthesis of amide derivatives 42–44: General procedure

To a stirred solution of (3-indenyl)acetic acids **33**, **36** or **37** (1 equiv) in dry THF was added in portions 1,1′-carbonyldiimidazole (2 equiv) under argon atmosphere. The resulting mixture was stirred at room temperature for 2 h and then a solution of pyrrolidine (2 equiv) in dry THF was added. After stirring for 18 h, the reaction mixture was evaporated, dissolved in EtOAc and washed with 1 N HCl. The organic layer was dried with anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel ($CH_2Cl_2$–MeOH mixtures of increasing polarity as eluent).

### *N*-[2-Methyl-3-(2-oxo-2-pyrrolidin-1-ylethyl)1*H*-inden-5-yl]naphthalene-2-sulfonamide 42

The above procedure was followed using the acetic acid derivative **33** (0.5 g, 1.27 mmol), 1,1′-carbonyldiimidazole (0.42 g, 2.54 mmol) and pyrrolidine (0.21 mL, 2.54 mmol) in dry THF (60 mL). The amide derivative **42** (0.2 g, 35%) was obtained as a yellow oil.

IR (thin film): ν(NH) 3063; ν(C=O) 1613; ν($SO_2$) 1323, 1156 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.65–1.84 (m, 4H), 2.02 (s, 3H), 3.12 (s, 2H), 3.32–3.43 (m, 6H), 6.84–6.89 (m, 1H), 7.01–7.05 (m, 1H), 7.13 (s, 1H), 7.39–7.52 (m, 3H), 7.68–7.79 (m, 4H), 8.33 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 14.4 ($CH_3$), 24.2 ($CH_2$), 26.2 ($CH_2$), 32.7 ($CH_2$), 42.2 ($CH_2$), 46.1 ($CH_2$), 46.8 ($CH_2$), 112.8 (CH), 117.6 (CH), 122.6 (CH), 123.2 (CH), 127.0 (CH), 127.6 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 129.2 (CH), 129.9, 131.9, 134.6, 135.2, 136.4, 138.9, 142.8, 147.1, 169.0 (C=O) ppm EI-MS *m*/*z*: 446 ($M^+$, 22%), 70 (100).

### *N*-[3-(2-Oxo-2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]naphthalene-2-sulfonamide 43

The above procedure was followed using the acetic acid derivative **36** (0.46 g, 1.21 mmol), 1,1′-carbonyldiimidazole (0.40 g, 2.42 mmol) and pyrrolidine (0.19 mL, 2.42 mmol) in dry THF (60 mL). The amide derivative **43** (0.37 g, 71%) was obtained as a yellow foamy solid.

Mp 126–127 °C. IR (thin film): ν(NH) 3245; ν(C=O) 1615; ν($SO_2$) 1326, 1156 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.80–2.00 (m, 4H), 3.18 (s, 2H), 3.30–3.50 (m, 4H), 6.30 (s, 1H), 6.95–6.99 (m, 1H), 7.05–7.09 (m, 2H), 7.40–7.58 (m, 2H), 7.64–7.86 (m, 4H), 8.38 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 24.4 ($CH_2$), 26.1 ($CH_2$), 35.0 ($CH_2$), 37.4 ($CH_2$), 46.0 ($CH_2$), 47.0 ($CH_2$), 113.6 (CH), 118.9 (CH), 122.5 (CH), 123.9 (CH), 127.1 (CH), 127.7 (CH), 128.5 (CH), 128.6 (CH), 129.0 (CH), 129.2 (CH), 132.2 (CH), 132.1, 134.4, 135.0, 136.0, 137.0, 141.4, 143.8, 168.8 (C=O) ppm. EI-MS *m*/*z*: 432 ($M^+$, 29%), 98 (100).

### 5-Chloro-3-methyl-*N*-[2-methyl-3-(2-oxo-2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]-1-benzothiophene-2-sulfonamide 44

The above procedure was followed using the acetic acid derivative **37** (0.22 g, 0.49 mmol), 1,1′-carbonyldiimidazole (0.16 g, 0.98 mmol) and pyrrolidine (0.08 mL, 0.98 mmol) in dry THF (24 mL). The amide derivative **44** (0.1 g, 41%) was obtained as a brown oil.

IR (thin film): ν(NH) 3079; ν(C=O) 1613; ν($SO_2$) 1335, 1157 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.78–1.98 (m, 4H), 2.07 (s, 3H), 2.36 (s, 3H), 3.22 (s, 2H), 3.36–3.44 (m, 6H), 6.82–6.88 (m, 1H), 7.08–7.14 (m, 2H), 7.32–7.38 (m, 1H), 7.60–7.64 (m, 2H), 7.82 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 12.2 ($CH_3$), 14.4 ($CH_3$), 24.2 ($CH_2$), 26.1 ($CH_2$), 32.4 ($CH_2$), 42.3 ($CH_2$), 46.4 ($CH_2$), 47.0 ($CH_2$), 113.3 (CH), 118.1 (CH), 123.1 (CH), 123.2 (CH), 123.5 (CH), 127.3 (CH), 129.6, 131.0, 134.5, 136.4, 136.6, 137.6, 139.4, 140.5, 143.0, 147.0, 169.2 (C=O) ppm. EI-MS *m*/*z*: 501 ($M^+$, 7%), 70 (100).

### *N*-[2-Methyl-3-(2-oxo-2-pyrrolidin-1-ylethyl)-1*H*-inden-7-yl]naphthalene-2-sulfonamide 45

A mixture of $SOCl_2$ (2 mL) and the acetic acid derivative **38** (0.15 g, 0.38 mmol) in dry $CH_2Cl_2$ (2 mL) was stirred at reflux for 2 h. The reaction mixture was concentrated under reduced pressure. The resulting brown solid was dissolved in dry $CH_2Cl_2$ (2.5 mL) and a solution of pyrrolidine (0.11 mL, 1.33 mmol) in dry $CH_2Cl_2$ (24 mL) was added. After stirring for 18 h, the reaction mixture was acidified with 1 N HCl and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, filtered and evaporated to dryness to afford the amide derivative **45** (80 mg, 47%) as a yellow oil. The product was used directly in the next step without further purification.

IR (thin film): ν(NH) 3107; ν(C=O) 1620; ν($SO_2$) 1336, 1162 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.82–1.98 (m, 7H), 2.97 (s, 2H), 3.40–3.60 (m, 6H), 6.58 (s, 1H), 7.54–7.62 (m, 4H), 7.85–7.98 (m, 4H), 8.32 (s, 1H) ppm. EI-MS *m*/*z*: 446 ($M^+$, 3%), 127 (42), 70 (100).

### Synthesis of amines derivatives 14–17: General procedure

To a stirred solution of $AlH_3$–$NMe_2Et$ (0.5 M in toluene, 2–4 equiv) in dry THF cooled to 0 °C was added *via* a hypodermic syringe a solution amide derivatives **42**, **43**, **44** or **45** (1 equiv) in dry THF previously cooled to 0 °C, under argon atmosphere. After stirring at 0 °C or room temperature for 30 min, the reaction mixture was hydrolyzed with water and 10% $H_2SO_4$ aqueous solution, stirred at room temperature and basified with 20% aqueous ammonia. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel ($CH_2Cl_2$–MeOH–$NH_3$ mixtures of increasing polarity as eluent).

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

The above procedure was followed using the amide derivative **42** (200 mg, 0.45 mmol) in dry THF (12 mL) and $AlH_3$–$NMe_2Et$ (0.5 M in toluene, 3.6 mL, 1.8 mmol) in dry THF (10 mL). The indene derivative **14** (70 mg, 36%) was obtained as a brown oil.

IR (thin film): ν(NH) 3250; ν($SO_2$) 1330, 1158 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.70–1.80 (m, 4H), 1.98 (s, 3H), 2.35–2.64 (m, 8H), 3.13 (s, 2H), 6.92–6.97 (m, 2H), 7.13–7.17 (m, 1H), 7.49–7.59 (m, 2H), 7.78–7.85 (m, 4H), 8.36 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 14.0 ($CH_3$), 23.4 ($CH_2$), 24.8 ($CH_2$), 42.1 ($CH_2$), 54.0 ($CH_2$), 54.7 ($CH_2$), 112.8 (CH), 118.3 (CH), 122.6 (CH), 123.5 (CH), 127.2 (CH), 127.7 (CH), 128.5 (CH), 128.6 (CH), 129.0 (CH), 129 (CH), 131.9, 134.2, 134.6, 135.0, 136.4, 139.7, 141.0, 147.4 ppm. EI-MS *m/z*: 432 ($M^+$, 2%), 84 (100). Found: C 64.98, H 6.32, N 6.00, S 6.31. Calcd for $C_{26}H_{28}N_2O_2S{\cdot}0.75CH_2Cl_2$: C 64.74, H 5.99, N 5.64, S 6.46%.

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

The above procedure was followed using the amide derivative **43** (180 mg, 0.42 mmol) in dry THF (7 mL) and $AlH_3$–$NMe_2Et$ (0.5 M in toluene, 1.7 mL, 0.85mmol) in dry THF (7 mL). The indene derivative **15** (100 mg, 57%) was obtained as a yellow solid.

Mp 119–120 °C. IR (thin film): ν(NH) 3056; ν($SO_2$) 1327, 1157 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.70–1.80 (m, 4H), 2.46–2.76 (m, 8H), 3.16 (s, 2H), 6.15 (s, 1H), 7.00–7.06 (m, 2H), 7.20–7.52 (m, 3H), 7.69–7.78 (m, 5H), 8.35 (s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 23.4 ($CH_2$), 27.1 ($CH_2$), 37.8 ($CH_2$), 54.0 ($CH_2$), 54.6 ($CH_2$), 113.8 (CH), 119.6 (CH), 122.5 (CH), 124.0 (CH), 127.1 (CH), 127.7 (CH), 128.4 (CH), 128.5 (CH), 129.0 (CH), 129.1 (CH), 129.6 (CH), 131.9, 134.2, 135.4, 136.6, 141.2, 141.8, 146.2 ppm. EI-MS *m/z*: 418 ($M^+$, 1%), 84 (100). Found: C 66.36, H 6.29, N 6.49, S 7.23. Calcd for $C_{25}H_{26}N_2O_2S{\cdot}2H_2O$: C 66.06, H 6.65, N 6.16, S 7.05%.

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

The above procedure was followed using the amide derivative **44** (160 mg, 0.32 mmol) in dry THF (5 mL) and $AlH_3$–$NMe_2Et$ (0.5 M in toluene, 1.6 mL, 0.8 mmol) in dry THF (5 mL). The indene derivative **16** (82 mg, 53%) was obtained as a brown solid. Chemical purity by HPLC: 99.6%

Mp 187–188 °C. IR (thin film): ν($SO_2$) 1333, 1157 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.80–1.86 (m, 4H), 2.02 (s, 3H), 2.38 (s, 3H), 2.39–2.62 (m, 6H), 3.18 (s, 2H), 6.86 (s, 1H), 7.02–7.10 (m, 1H), 7.15–7.12 (m, 1H), 7.20–7.38 (m, 2H), 7.63–7.67 (m, 2H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 Hz): $\delta$ 12.0 ($CH_3$), 13.9 ($CH_3$), 23.2 ($CH_2$), 24.4 ($CH_2$), 42.1 ($CH_2$), 53.8 ($CH_2$), 54.4 ($CH_2$), 112.1 (CH), 117.9 (CH), 123.1 (CH), 123.5 (CH), 127.3 (CH), 131.2, 133.8, 134.6, 136.0, 137.0, 137.8, 139.5, 140.5, 141.1, 147.7 ppm. ESI-HRMS calcd for $C_{25}H_{28}N_2O_2S_2Cl$ $[M + H]^+$: 487.1275; found: 487.1274.

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

The above procedure was followed using the amide derivative **45** (130 mg, 0.29 mmol) in dry THF (5 mL) and $AlH_3$–$NMe_2Et$ (0.5 M in toluene, 1.16 mL, 0.58 mmol) in dry THF (5 mL). The indene derivative **17** (7 mg, 6%) was obtained as a yellow oil. Chemical purity by HPLC: 89.0%

IR (thin film): ν(NH) 3261; ν($SO_2$) 1335, 1160 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.90 (m, 4H), 1.99 (s, 3H), 2.64–2.76 (m, 8H), 3.08 (s, 2H), 6.97- 6.99 (m, 1H), 7.05–7.16 (m, 2H), 7.55–7.65 (m, 2H), 7.77–7.80 (m, 1H), 7.85–7.90 (m, 3H), 8.35 (d, $J$ = 1.6 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 100.6 Hz): $\delta$ 14.1 ($CH_3$), 23.7 ($CH_2$), 40.5 ($CH_2$), 54.2 ($CH_2$), 54.9 ($CH_2$), 116.4 (CH), 118.8 (CH), 122.5 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 129.0 (CH), 129.1 (CH), 129.5 (CH), 129.6 (CH), 131.6, 132.2, 135.1, 135.5, 136.7 ppm.

**Attempted preparation of sulfonamide 46**

**Experiment 1.** Pd/C (10 wt.%, 25 mg) was added to a solution of acetic acid derivative **39** (220 mg, 0.46 mmol) in absolute EtOH (15 mL). The resulting suspension was hydrogenated at atmospheric pressure and room temperature for 4 h. The reaction mixture was filtered trough Celite® and evaporated to dryness to obtain decomposition products.

**Experiment 2: *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.** To a stirred solution of indanone sulfonamide **28** (1.0 g, 2.85 mmol) in dry THF (15 mL) cooled to −78 °C was added *via* a hypodermic syringe LDA mono-THF complex solution (1.5 M in cyclohexane, 6.7 mL, 9.98 mmol) under argon atmosphere. After stirring at −78 °C for 1 h, the slurry was allowed to warm to room temperature for 4 h. The resulting dark red solution was cooled to −40 °C and a solution of benzyl bromide (0.85 mL, 7.13 mmol) in dry THF (10 mL) was added. The resultant mixture was stirred at room temperature for 18 h. The reaction mixture was quenched by addition of brine (20 mL) and 2.5 N HCl (20 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (hexanes–EtOAc mixtures of increasing polarity as eluent) to afford the benzylindanone derivatives **49** (660 mg, 52%) and **50** (160 mg, 11%) as off-white solids.

**49**: Mp 145–146 °C. IR (KBr): ν(NH) 3243; ν(C=O) 1709; ν($SO_2$) 1334, 1157 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.17 (s, 3H), 2.63 (d, $J$ = 17.1 Hz, 1H), 2.73 (d, $J$ = 13.5, 1H), 2.94 (d, $J$ = 13.5 Hz), 3.12 (d, $J$ = 17.4 Hz, 1H), 7.02–7.11 (m, 5H), 7.18–7.22 (m, 2H), 7.37–7.44 (m, 2H), 7.54–7.65 (m, 2H), 7.72–7.76 (m, 1H), 7.85–7.89 (m, 3H), 8. 37 (d, $J$ = 1.8 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 Hz): $\delta$ 24.8 ($CH_3$), 38.8 ($CH_2$), 43.7 ($CH_2$), 51.3, 116.7 (CH), 122.4 (CH), 126.7 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 128.9 (CH), 129.3 (CH), 129.4 (CH), 129.7 (CH), 129.9 (CH), 130.4 (CH), 132.3, 135.3, 136.0, 136.4, 137.1, 137.8, 149.7, 210.4 (C=O) ppm. ESI-HRMS calcd for $C_{27}H_{24}NO_3S$ $[M + H]^+$ 442.1471; found 442.1479.

**50**: Mp 119–120 °C. IR (KBr): ν(NH) 3031; ν(C=O) 1707; ν($SO_2$) 1352, 1164 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.19 (s, 3H), 2.67 (d, $J$ = 17.4 Hz, 1H), 2.73 (d, $J$ = 13.5 Hz, 1H), 2.95 (d, $J$ = 13.5 Hz, 1H), 3.15 (d, $J$ = 17.7 Hz, 1H), 4.76 (s, 2H), 7.03–7.06 (m, 3H), 7.12–7.20 (m, 5H), 7.23–7.29 (m, 3H), 7.53–7.70 (m 4H), 7.87–7.95 (m, 4H), 8.24 (d, $J$ = 1.8 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 Hz): $\delta$ 24.7 ($CH_3$), 39.1 ($CH_2$), 44.0 ($CH_2$), 51.3, 55.1 ($CH_2$), 123.1 (CH), 123.4 (CH), 126.8 (CH), 127.3 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.8 (CH), 129.3 (CH), 129.6 (CH), 129.7 (CH), 130.4 (CH), 132.5, 135.3, 135.6, 135.7, 136.8, 136.9, 137.7 (CH), 138.9, 152.3, 210.1 (C=O) ppm. ESI-HRMS calcd for $C_{34}H_{30}NO_3S$ $[M + H]^+$ 532.1940; found 532.1949.

### 5-$HT_6$ binding assay

Membranes of HEK-293 cells expressing the $5HT_6$ human recombinant receptor were supplied by Receptor Biology. In these membranes the receptor concentration was 2.18 pmol $mg^{-1}$ protein and the protein concentration was 9.17 mg $mL^{-1}$. The experimental protocol followed the method of B. L. Roth *et al.* with slight modifications.[18] The commercial membrane was diluted (dilution 1 : 40) with the binding buffer: 50 mM Tris-HCl, 10 mM $MgCl_2$, 0.5 mM EDTA (pH 7.4). The radioligand used was [$^3$H]-LSD at a concentration of 2.7 nM with a final volume of 200 µl. Incubation was initiated by adding 100 µl of the membrane suspension (≈22.9 µg membrane protein), and continued for 60 min at a temperature of 37 °C. Incubation was terminated by fast filtration through glass fibre filters in a Harvester Brandel Cell manufactured by Schleicher & Schuell GF 3362 pre-treated with a 0.5% polyethylenimine solution. The filters were washed three times with 3 mL of Tris-HCl 50 mM pH 7.4 buffer. The filters were transferred to phials and to each phial 5 mL of liquid scintillation cocktail Ecoscint H was added. The phials were allowed to reach equilibrium for several hours before being counted in a Wallac Winspectral 1414 scintillation counter. Non-specific binding was determined in the presence of 100 µM serotonin. The tests of preferred compounds were performed in triplicate. The inhibition constants ($K_i$, nM) were calculated by non-linear regression analysis using the program EBDA/LIGAND.[19] A linear regression line of data points was plotted, from which the concentration of competing ligand which displaces 50% of the specific binding of the radioligand ($IC_{50}$ value) was determined, and the $K_i$ value was determined based upon the Cheng–Prusof equation: $K_i = IC_{50}/(1 + L/K_D)$ were $L$ is the concentration of free radioligand used in the assay and $K_D$ is the dissociation constant of the radioligand for the receptor.

### Adenylyl cyclase activity assay

Functional effects of the compounds were evaluated by cAMP measurements on HEK-293F cells stably expressing the human 5-$HT_6$ receptor using a HTRF assay format.[20]

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## References

1 (*a*) M. Sharma and S. M. Ray, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6790–6796; (*b*) J. W. Huffman and L. W. Padgett, *Curr. Med. Chem.*, 2005, **12**, 1395–1411; (*c*) J. W. Huffman, R. Mabon, M. -J. Wu, J. Lu, R. Hart, D. P. Hurst, P. H. Reggio, J. L. Wiley and B. R. Martin, *Bioorg. Med. Chem.*, 2003, **11**, 539–549; (*d*) T. M. Böhme, C. Keim, K. Kreutzmann, M. Linder, T. Dingermann, G. Dannhardt, E. Mutschler and G. Lambrecht, *J. Med. Chem.*, 2003, **46**, 856–867; (*e*) E. T. Goluboff, *Expert Opin. Investig. Drugs*, 2001, **10**, 1875–1882; (*f*) P. H. Reggio, S. Basu-Dutt, J. Barnett-Norris, M. T. Castro, D. P. Hurst, H. H. Seltzman, M. J. Roche, A. F. Gilliam, B. F. Thomas, L. A. Stevenson, R. G. Pertwee and M. E. Abood, *J. Med. Chem.*, 1998, **41**, 5177–5187; (*g*) E. M. Coyanis, J.-L. Panayides, M. A. Fernandes, C. B. de Koning and W. A. L. van Otterlo, *J. Organomet. Chem.*, 2006, **69**, 5222–5239.

2 Adis International Limited, *Drugs R&D*, 2004, **5**, 220–226.

3 I.-M. Karaguni, K.-H. Glüsenkamp, A. Langerak, C. Geisen, V. Ullrich, G. Winde, T. Möröy and O. Müller, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 709–713.

4 (*a*) O. Müller, E. Gourzoulidou, M. Carpintero, I. -M. Karaguni, A. Langerak, C. Herrmann, T. Möröy, L. Klein-Hitpaß and H. Waldmann, *Angew. Chem., Int. Ed.*, 2004, **43**, 450–454; (*b*) H. Waldmann, I. -M. Karaguni, M. Carpintero, E. Gourzoulidou, C. Herrmann, C. Brockmann, H. Oschkinat and O. Müller, *Angew. Chem., Int. Ed.*, 2004, **43**, 454–458.

5 R. Kolanos, U. Siripurapu, M. Pullagurla, M. Riaz, V. Setola, B. L. Roth, M. Dukata and R. A. Glennon, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1987–1991.

6 D. Sikazwe, M. L. Bondarev, M. Dukat, J. B. Rangisetty, B. L. Roth and R. A. Glennon, *J. Med. Chem.*, 2006, **49**, 5217–5225.

7 R. Mercè, B. Andaluz and J. Frigola, *World Pat.* WO 03/042175 A1, 2003.

8 (*a*) J. Holenz, R. Mercè, J. L. Díaz, X. Guitart, X. Codony, A. Dordal, G. Romero, A. Torrens, J. Mas, B. Andaluz, S. Hernández, X. Monroy, E. Sánchez, E. Hernández, R. Pérez, R. Cubí, O. Sanfeliu and H. Buschmann, *J. Med. Chem.*, 2005, **48**, 1781–1795; (*b*) K. Alex, N. Schwarz, V. Khedkar, I. A. Sayyed, A. Tillack, D. Michalik, J. Holenz, J. L. Díaz and M. Beller, *Org. Biomol. Chem.*, 2008, **6**, 1802–1807.

9 (*a*) J. Holenz, P. J. Pauwels, J. L. Díaz, R. Mercè, X. Codony and H. Buschmann, *Drug Discovery Today*, 2006, **11**, 283–299; (*b*) D. J. Heal, S. L. Smith, A. Fisas, X. Codony and H. Buschmann, *Pharmacol. Ther.*, 2008, **117**, 207–231.

10 (*a*) H. Tsukamoto, T. Ueno and Y. Kondo, *Org. Lett.*, 2007, **9**, 3033–3036 and references therein; (*b*) P. V. Ivchenko, I. E. Nifant'ev, Y. N. Luzikov and S. G. Mkoyan, *Synthesis*, 2007, 1038–1046.

11 (*a*) M. W. Rathke and M. Nowak, *J. Org. Chem.*, 1985, **50**, 2624–2626; (*b*) F. Bonadies, A. Cardilli, A. Lattanzi, L. R. Orelli and A. Scettri, *Tetrahedron Lett.*, 1994, **35**, 3383–3386; (*c*) R. A. Moss and P. K. Gong, *Tetrahedron Lett.*, 2003, **44**, 7845–7848; (*d*) B. M. Trost and L. H. Latimer, *J. Org. Chem.*, 1977, **42**, 3212–3214.

12 (*a*) MDS Pharma Services-Discovery. See the following website: http://www.mdsps.com; (*b*) Assay Package – LeadProfilingScreen®: http://discovery.mdsps.com/Catalog/Discovery/AssayPackage.aspx?id=68.

13 M. Adamczyk and D. S. Watt, *J. Org. Chem.*, 1984, **49**, 4226–4237.

14 D. L. Musso, F. R. Cochran, J. L. Kelley, E. W. McLean, J. L. Selph, G. C. Rigdon, G. F. Orr, R. G. Davis, B. R. Cooper, V. L. Styles, J. B. Thompson and W. R. Hall, *J. Med. Chem.*, 2003, **46**, 399–408.

15 E. Alcalde, M. Alemany and M. Gisbert, *Tetrahedron*, 1996, **52**, 15171–15188.

16 I. Smonou and M. Orfanopoulos, *Synth. Commun.*, 1990, **20**, 1387–1397.

17 P. M. G. Bavin, C. R. Ganellin, J. L. Loynes and R. G. W. Spickett, *J. Med. Chem.*, 1969, **12**, 513–516.
18 B. L. Roth, S. C. Craigo, M. S. Choudhary, A. Uluer, F. J. Monsma, Jr., Y. Shen, H. Y. Meltzer and D. R. Sibley, *J. Pharmacol. Exp. Ther.*, 1994, **268**, 1403–1410.
19 P. J. Munson and D. Rodbard, *Anal. Biochem.*, 1980, **107**, 220–239.
20 (*a*) A. Fisas, X. Codony, G. Romero, A. Dordal, J. Giraldo, R. Mercè, J. Holenz, D. Heal, H. Buschmann and P. J. Pauwels, *Br. J. Pharmacol.*, 2006, **148**, 973–983; (*b*) G. Romero, E. Sanchez, M. Pujol, P. Perez, X. Codony, J. Holenz, H. Buschmann and P. J. Pauwels, *Br. J. Pharmacol.*, 2006, **148**, 1133–1143; (*c*) G. Romero, M. Pujol, P. Perez, H. Buschmann and P. J. Pauwels, *J. Pharmacol. Toxicol. Methods*, 2007, **55**, 144–150.

 

## Supplementary Data

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

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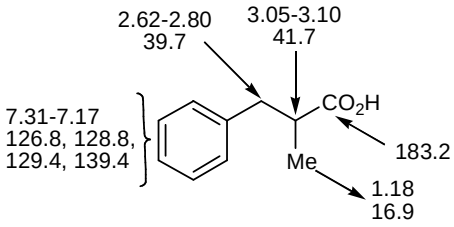
## ❖ $^{1}$H NMR AND $^{13}$C NMR ASSIGNMENTS

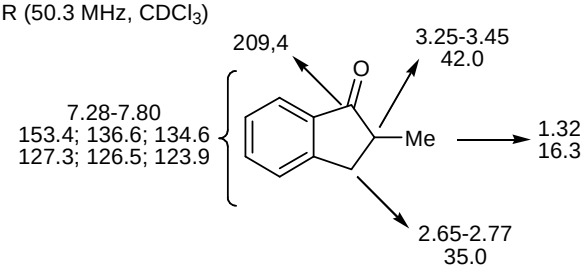
- **2-Methyl-3-phenylpropanoic acid 18**

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



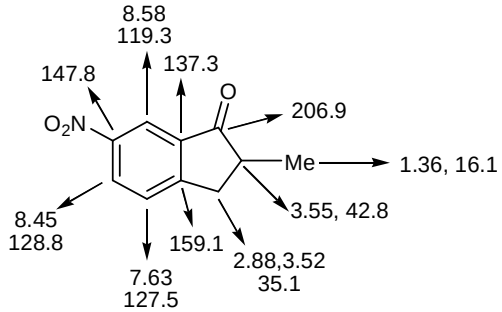

- **2-Methylindan-1-one 19**

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



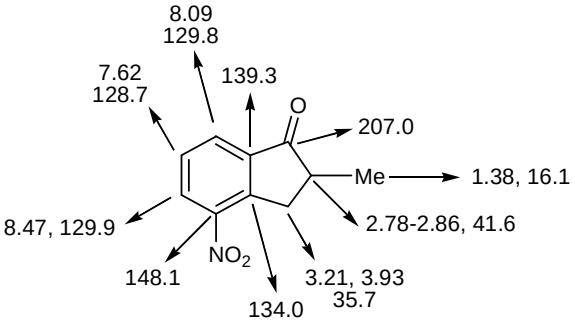

- **2-Methyl-6-nitroindan-1-one 20**

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



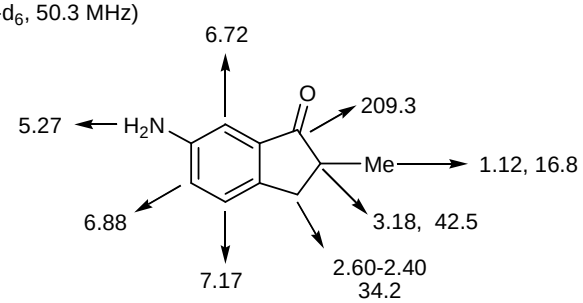

- **2-Methyl-4-nitroindan-1-one 21**

$^{1}$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**

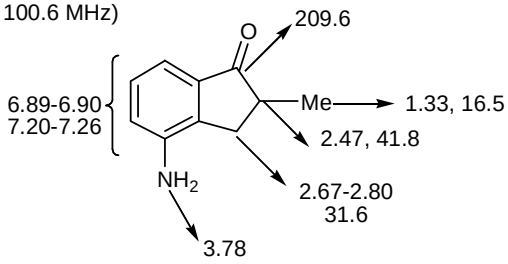
$^{1}$H NMR (DMSO-$d_6$, 200 MHz)
$^{13}$C NMR (DMSO-$d_6$, 50.3 MHz)




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

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

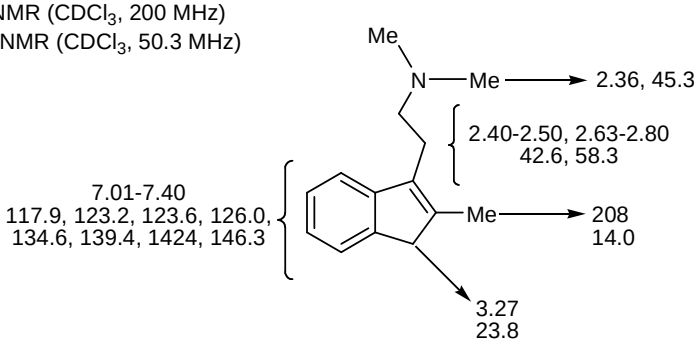
$^{1}$H NMR ($CDCl_3$, 200 MHz)
$^{13}$C ($CDCl_3$, 100.6 MHz)




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)



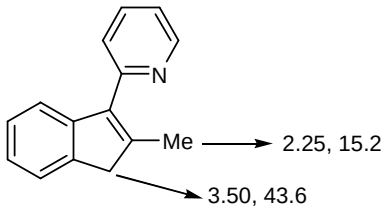

- **2-(2-Methyl-1*H*-inden-3-yl)pyridine 26**

$^{1}$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

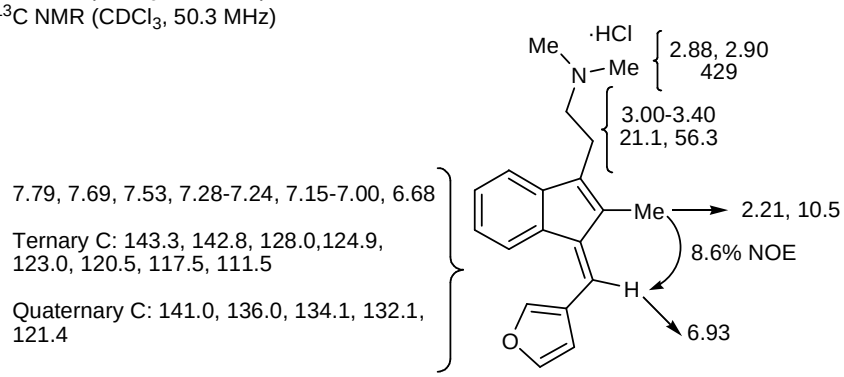
Ternary C: 1496, 136.1, 126.1,
124.1, 123.2, 121.6, 119.7

Quaternary C: 145.2, 143.8, 142.1



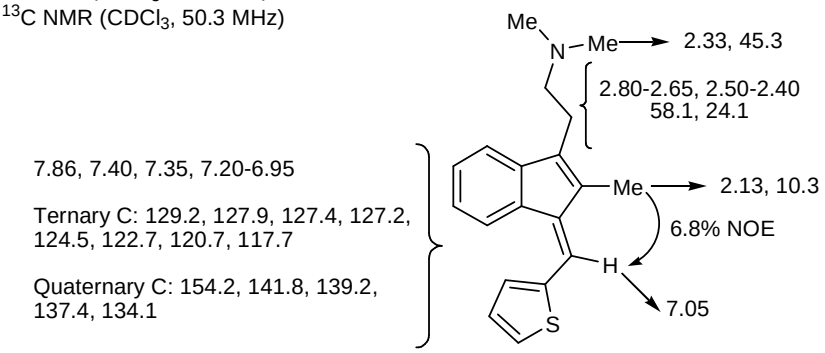
- **2-[(1*Z*)-1-(3-Furylmethylidene)-2-methyl-1*H*-inden-3-yl]-*N*,*N*-dimethylethanamine hydrochloride 8**

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



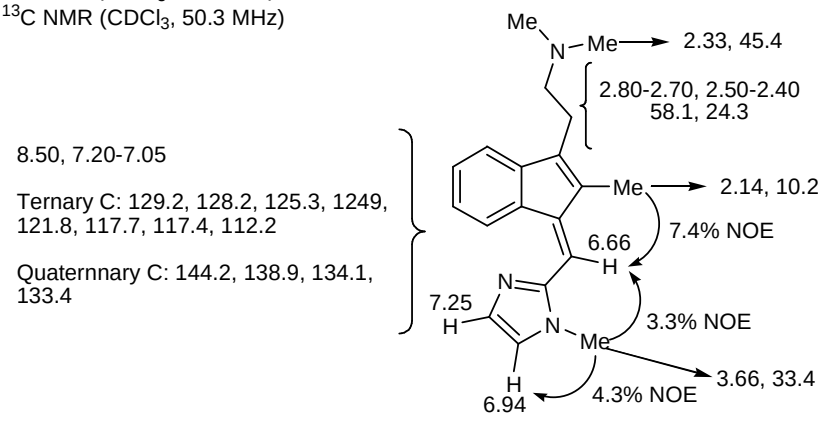

- ***N*,*N*-Dimethyl-2-[(1*Z*)-2-methyl-1-(2-thienylmethylidene)-1*H*-inden-3-yl]ethanamine 9**

$^{1}$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)



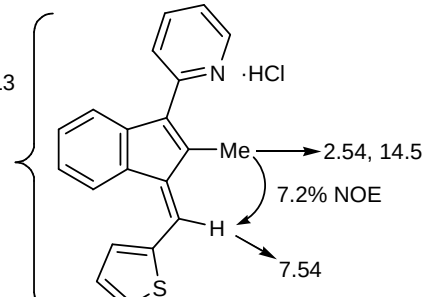
- **2-[(1*Z*)-2-Methyl-1-(2-thienylmethylidene)-1*H*-inden-3-yl]pyridine hydrochloride 11·HCl**

$^{1}$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

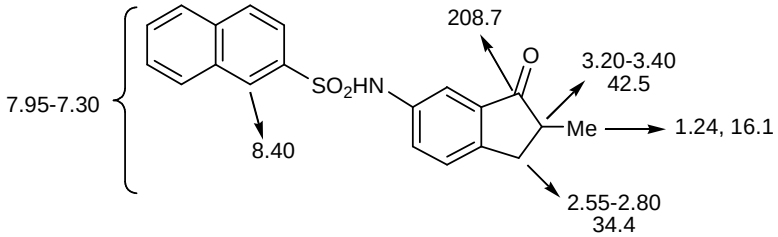
Ternary C: 133.5, 131.8, 129.6, 128.7, 128.0, 125.9, 123.3, 120.0

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**

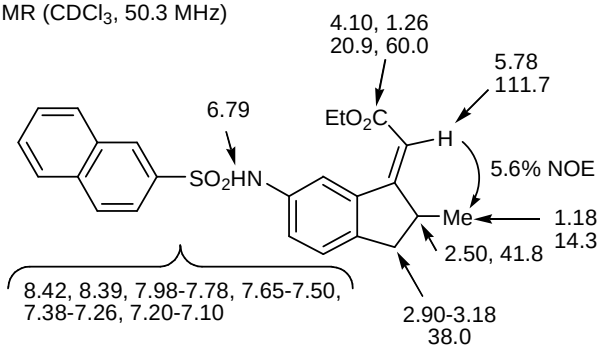
$^{1}$H, $^{13}$C NMR ($CDCl_3$, 200 MHz)




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

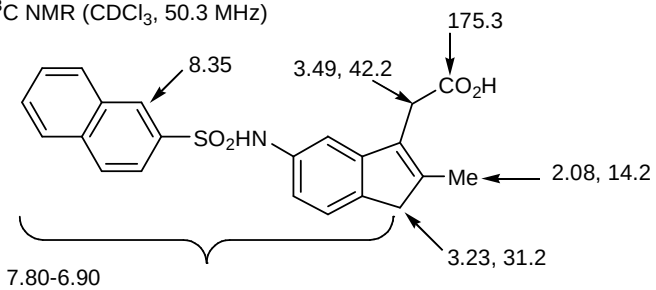
- **Ethyl (2*Z*)-{2-methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetate 32**

$^{1}$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**

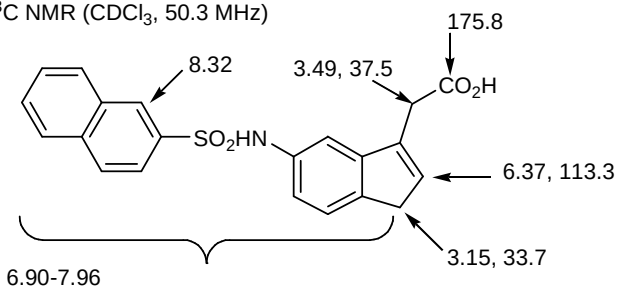
$^1$H NMR ($CDCl_3$, 200 MHz)
$^{13}$C NMR ($CDCl_3$, 50.3 MHz)




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**

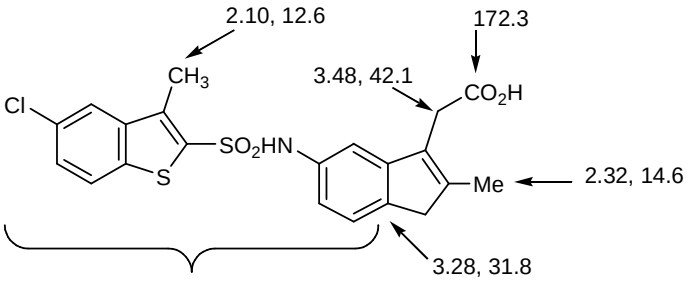
$^1$H NMR ($CDCl_3$, 200 MHz)
$^{13}$C NMR ($CDCl_3$, 50.3 MHz)




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**

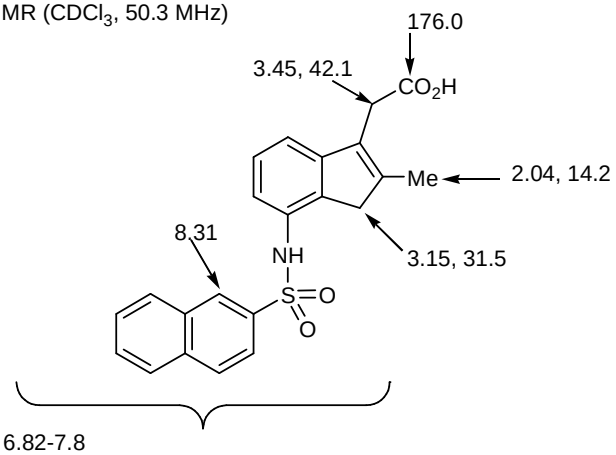
$^1$H NMR ($CDCl_3$, 200 MHz)
$^{13}$C NMR ($CDCl_3$, 50.3 MHz)




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**

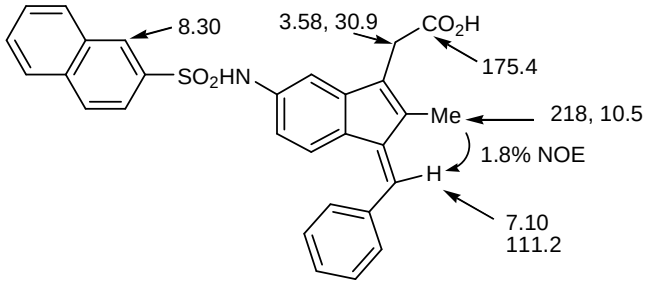
$^1$H NMR ($CDCl_3$, 200 MHz)
$^{13}$C NMR ($CDCl_3$, 50.3 MHz)




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

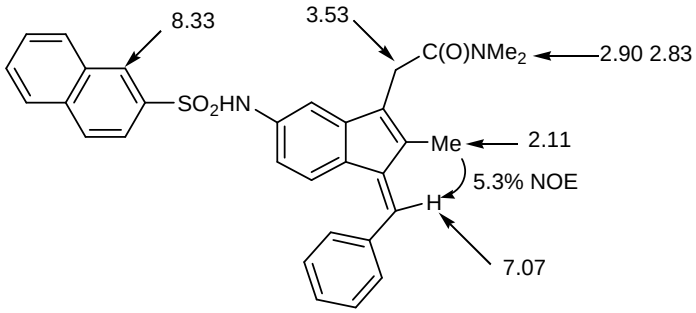
- **{(1*Z*)-1-Benzylidene-2-methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetic acid 39**

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



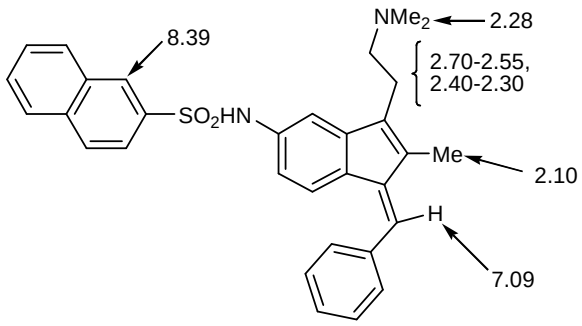

- ***N*,*N*-Dimethyl-2-{(1*Z*)-1-benzylidene-2-methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetamide 40**

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



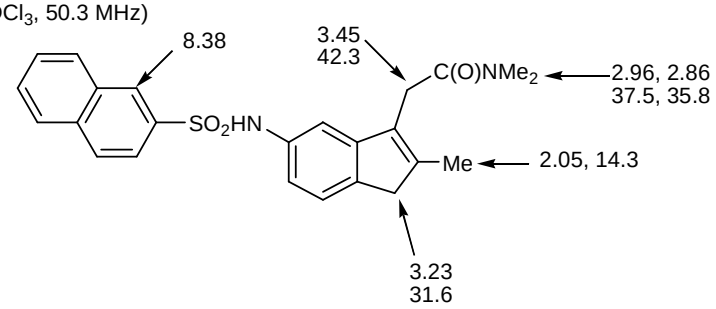
- ***N*-{(1*Z*)-1-Benzylidene-3-[2-(dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 12**

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



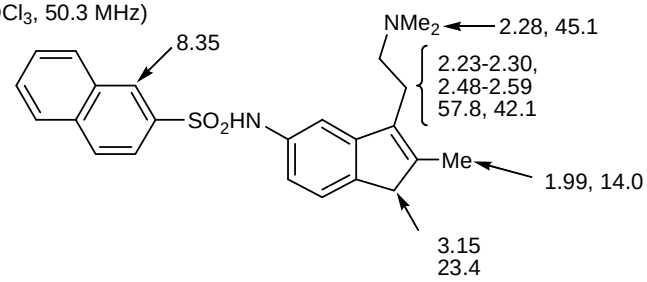

- ***N*,*N*-Dimethyl-2-{2-methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetamide 41**

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



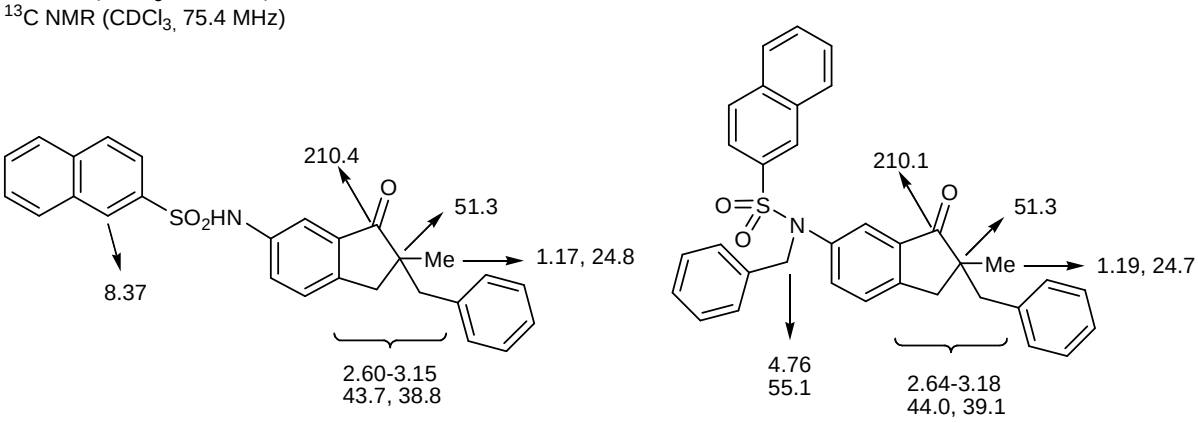

- ***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 13**

$^1$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**

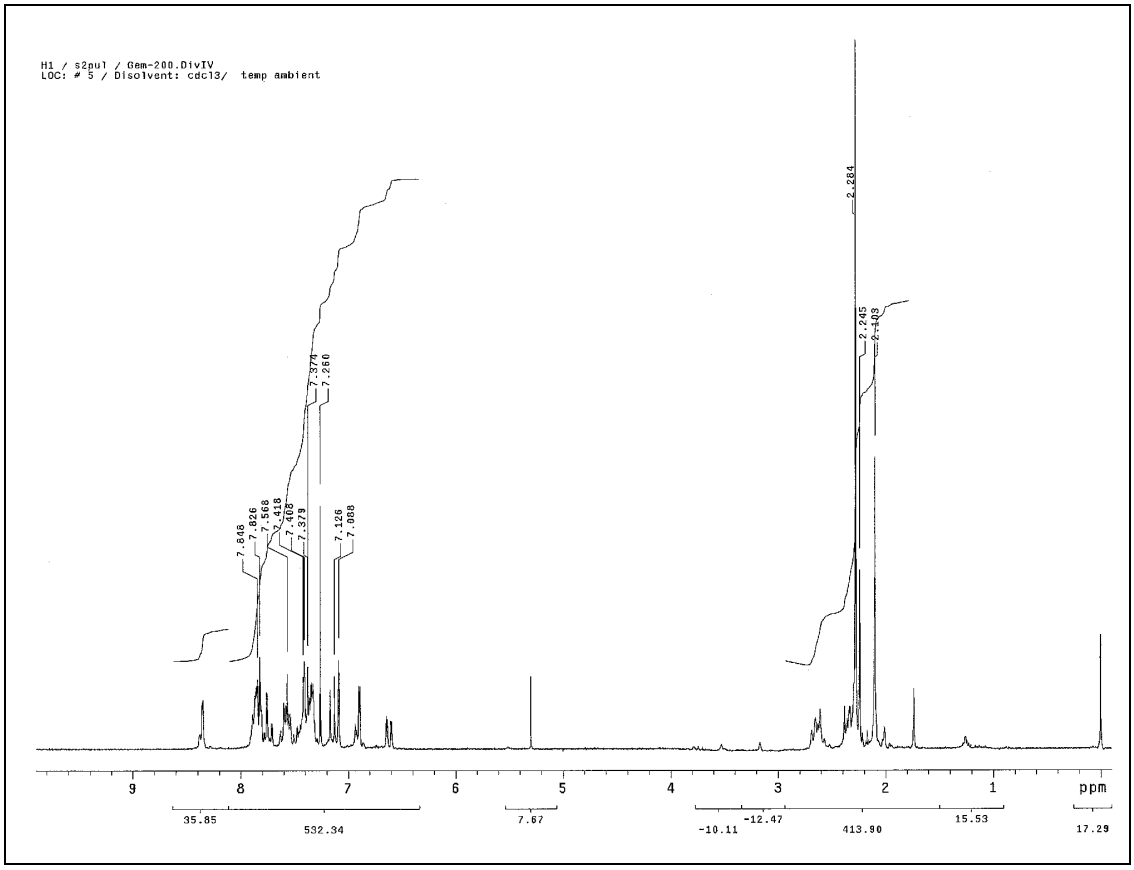
$^1$H NMR ($CDCl_3$, 300 MHz)
$^{13}$C NMR ($CDCl_3$, 75.4 MHz)



## ❖ NMR SPECTRA OF TARGETED COMPOUNDS

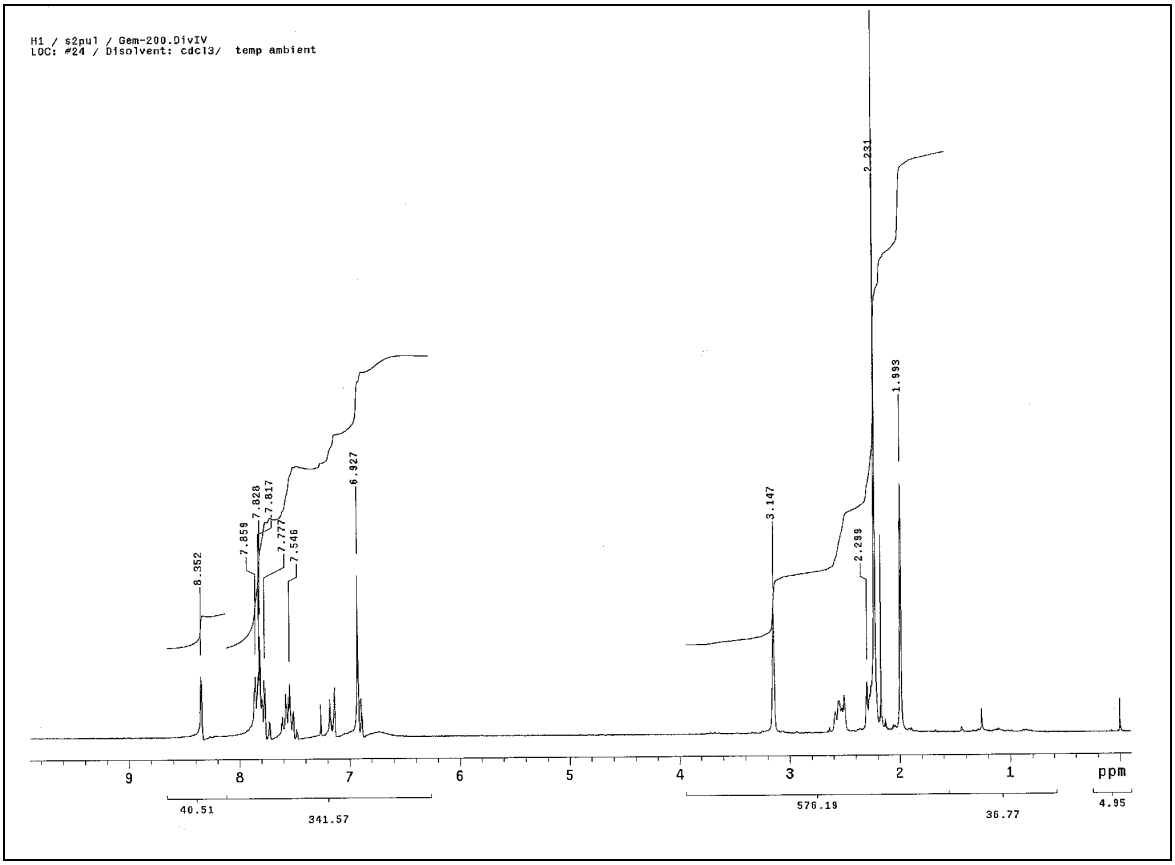
- ***N*-{(1*Z*)-1-Benzylidene-3-[2-(dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 12**

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

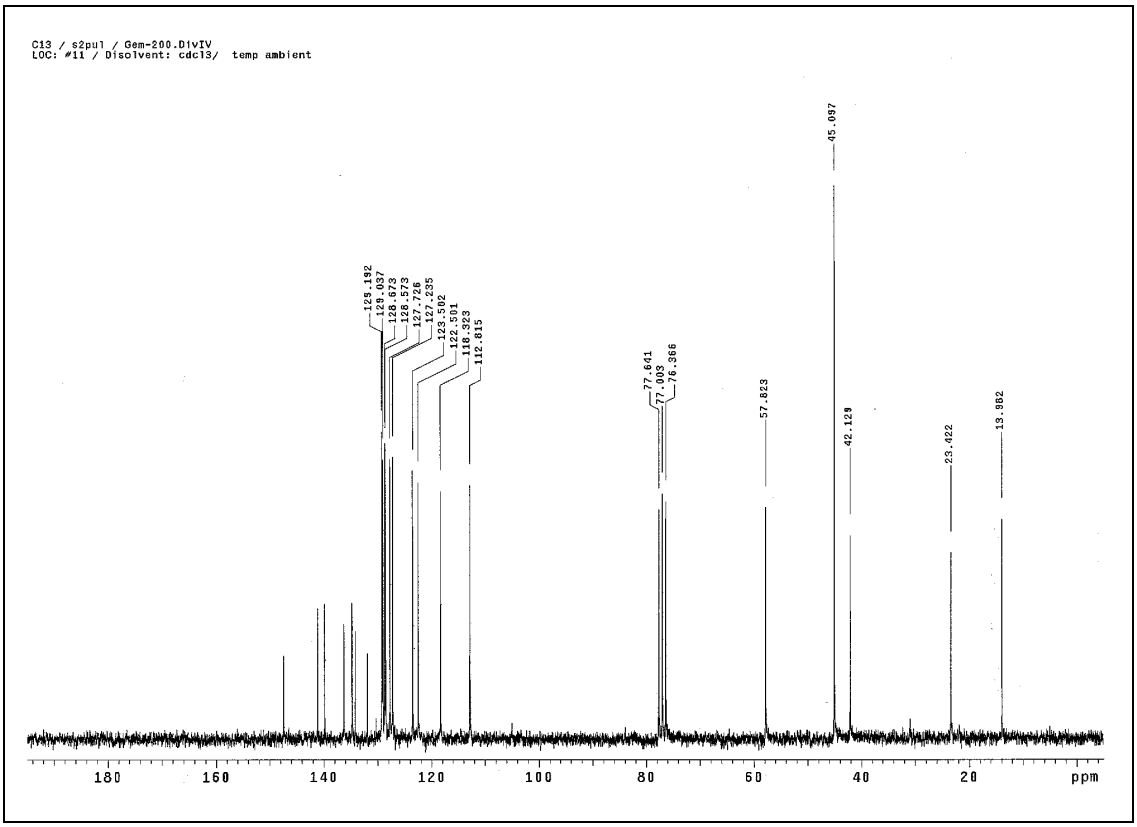


- ***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 13**

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

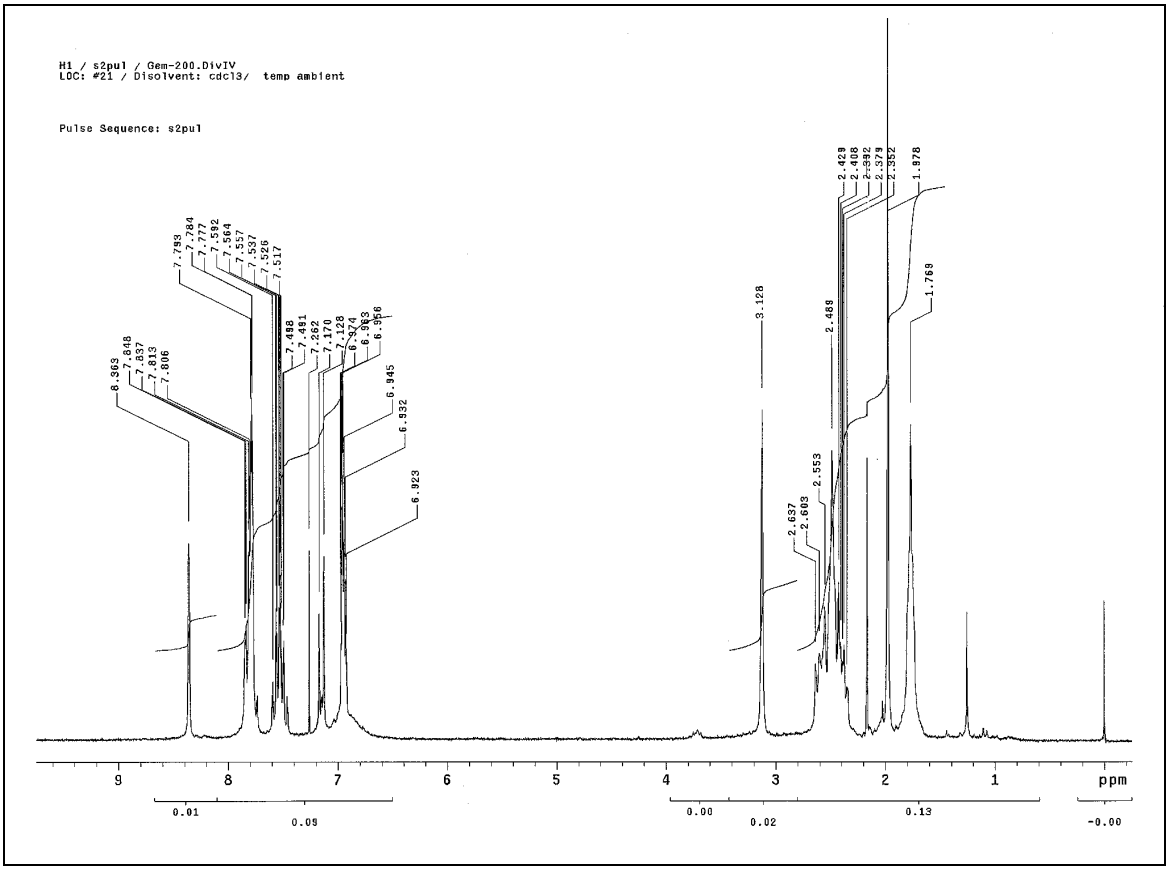



$^{13}$C NMR (50.3 MHz, $CDCl_3$)

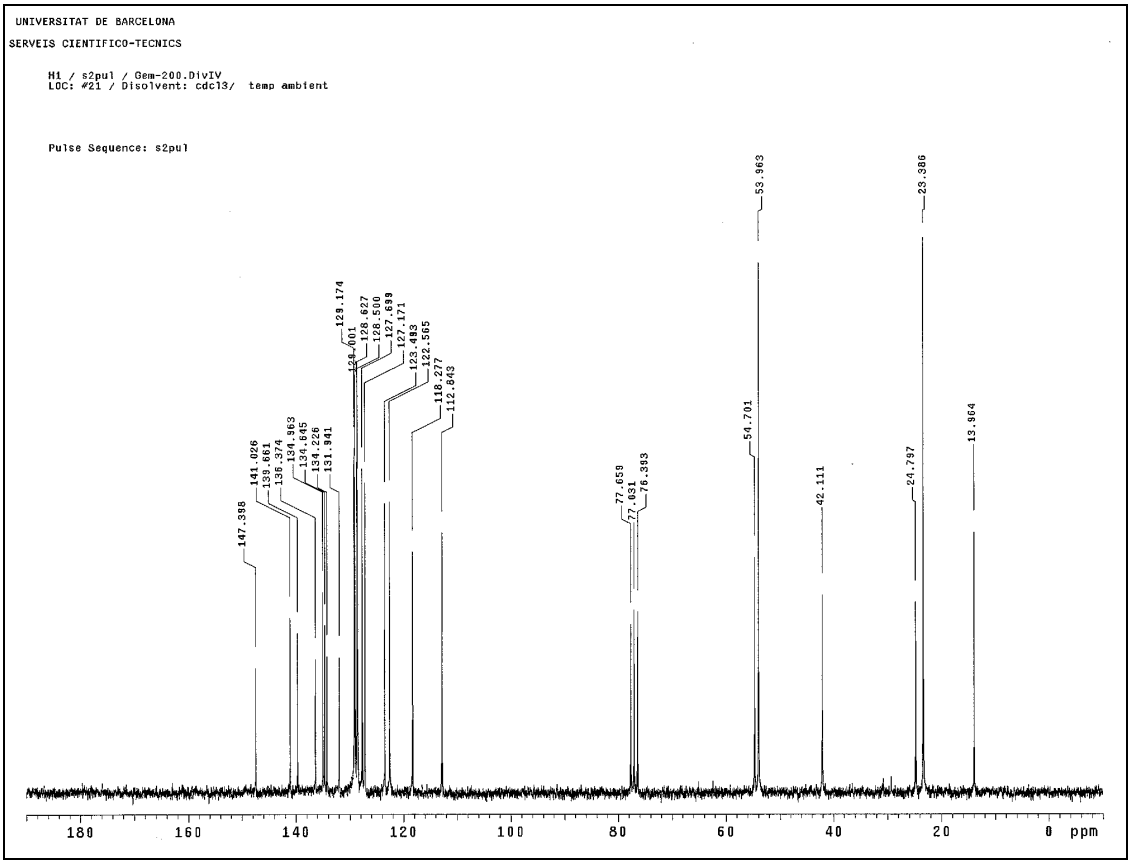


- ***N*-[2-Methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]naphthalene-2-sulfonamide 14**

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

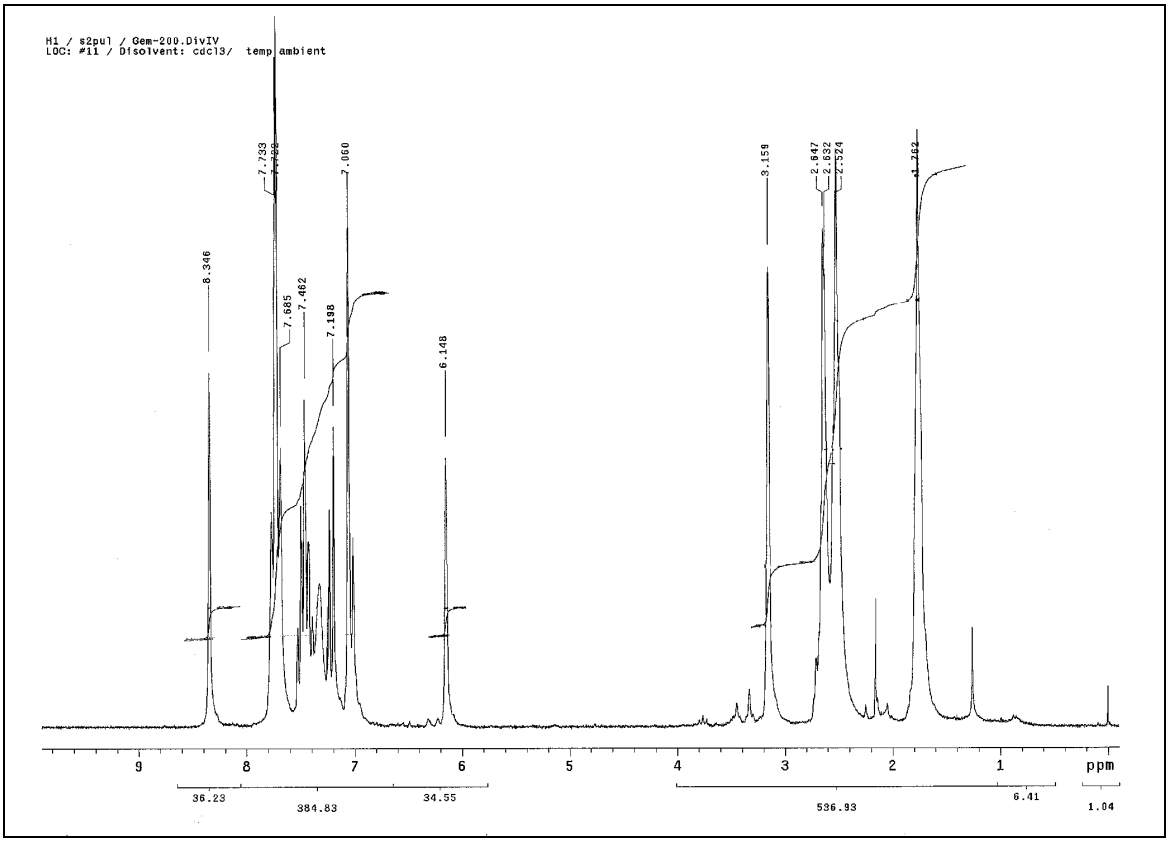



$^{13}$C NMR (50.3 MHz, $CDCl_3$)

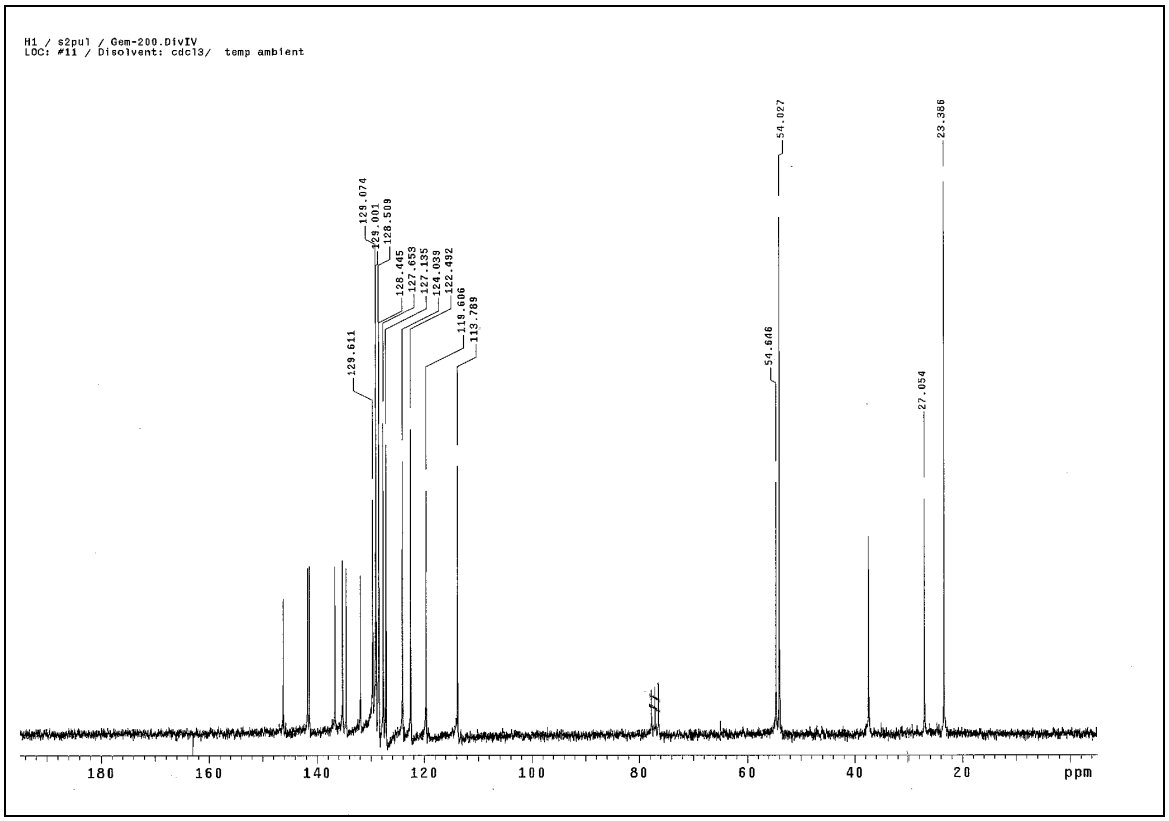


- ***N*-[3-(2-Pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]naphtalene-2-sulfonamide 15**

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

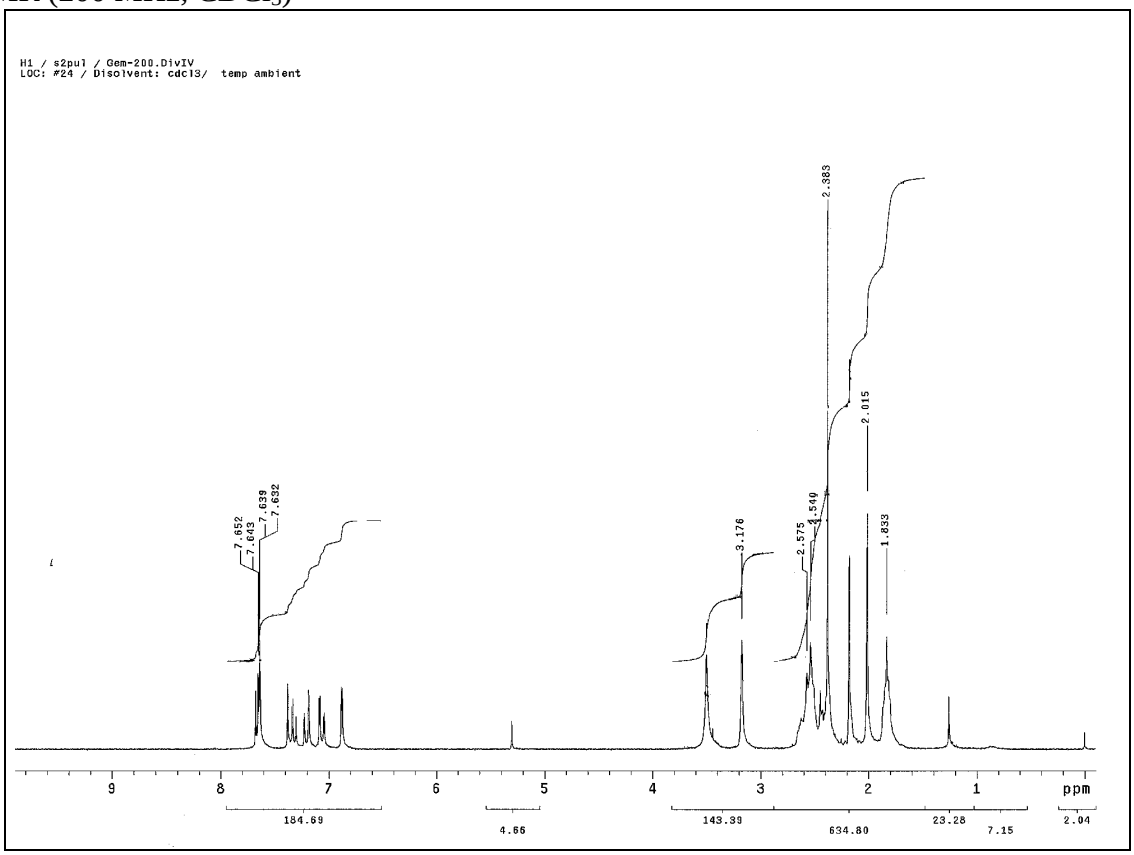



$^{13}$C NMR (50.3 MHz, $CDCl_3$)

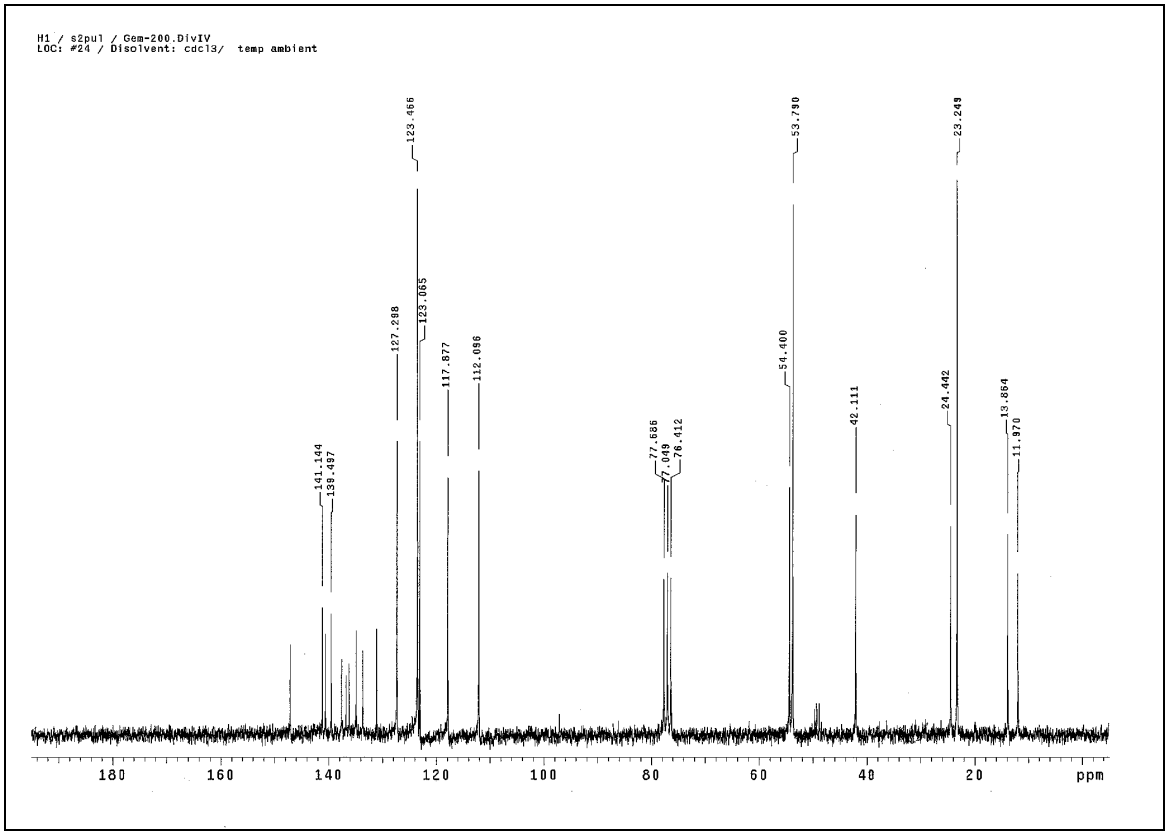


- **5-Chloro-3-methyl-*N*-[2-methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]-1-benzothiophene-2-sulfonamide 16**

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

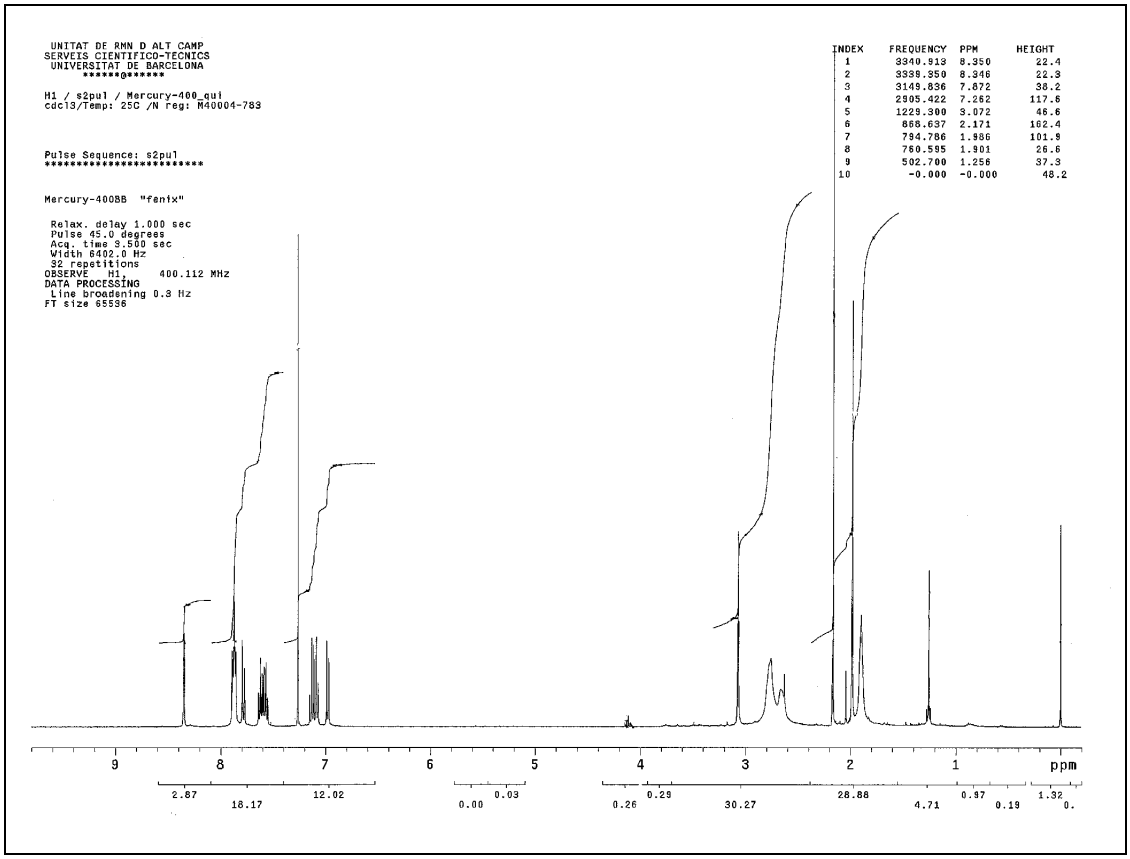



$^{13}$C NMR (50.3 MHz, $CDCl_3$)

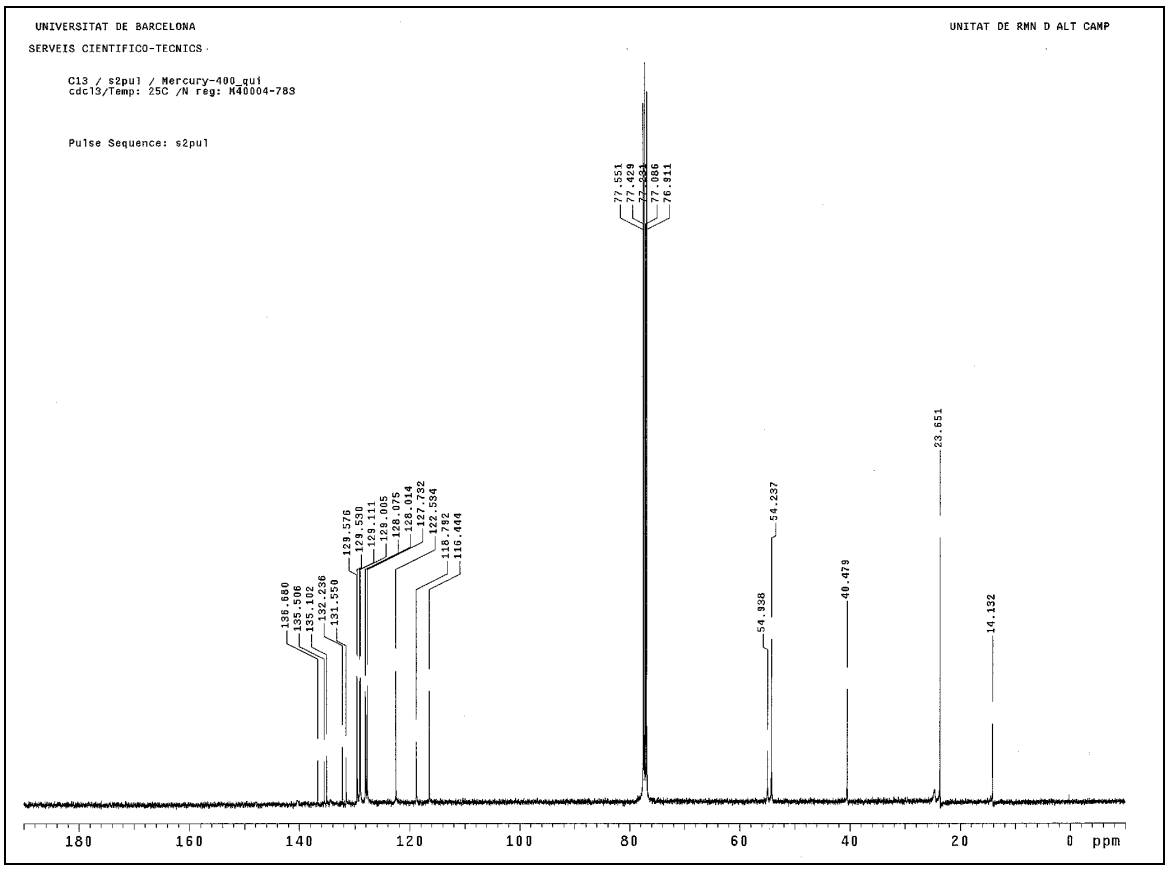


- ***N*-[2-Methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-7-yl]naphthalene-2-sulfonamide 17**

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

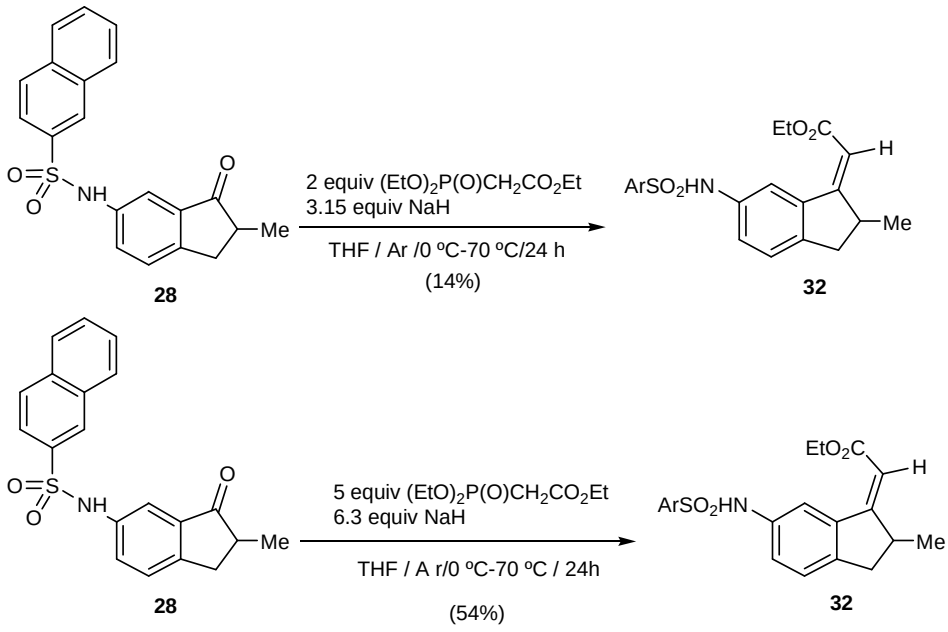



$^{13}$C NMR (100.6 MHz, $CDCl_3$)

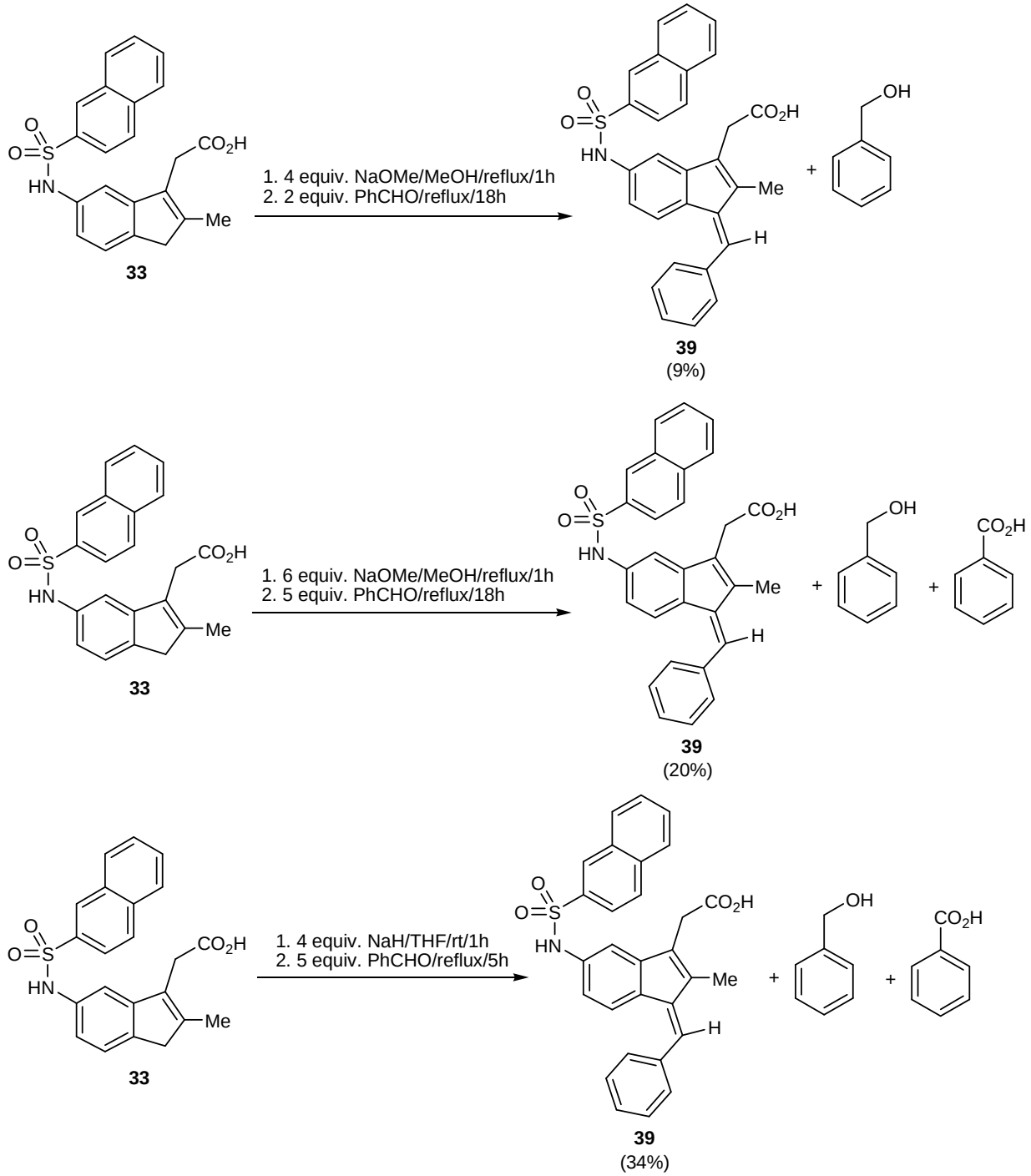


## ❖ ASSAYS RELATED WITH THE PREPARATION OF INDENES 12 AND 13

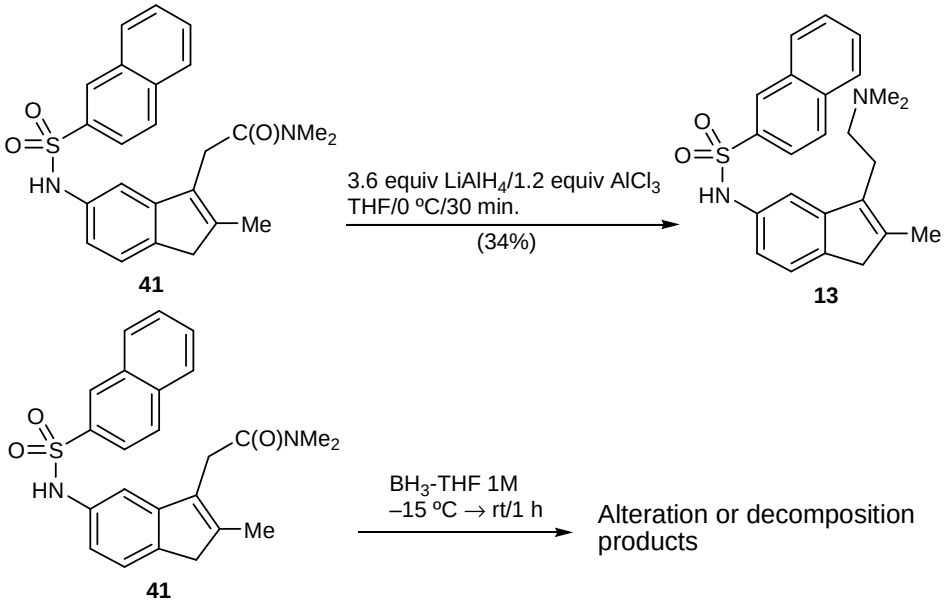
- **Ethyl {2-methyl-5-[(2-naphthylsulfonyl)amino]-1*H*-inden-3-yl}acetate 32**



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



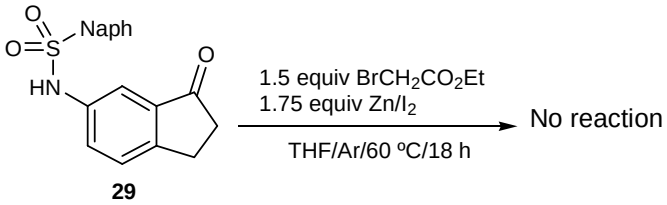
- ***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 13**



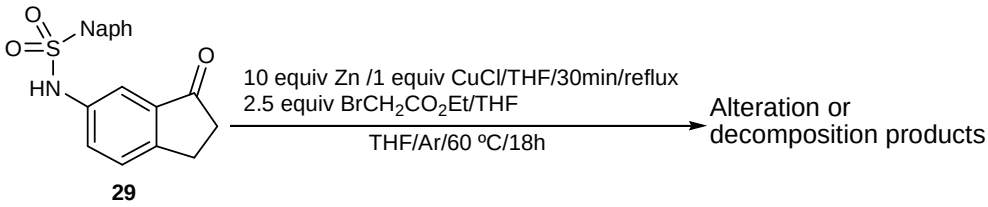
## ❖ ASSAYS RELATED WITH THE PREPARATION OF INDENES 14–17

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

  - **Reformatsky reaction**

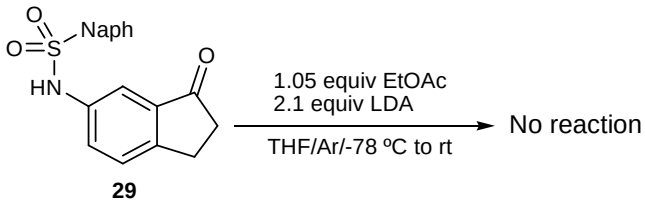



**29**



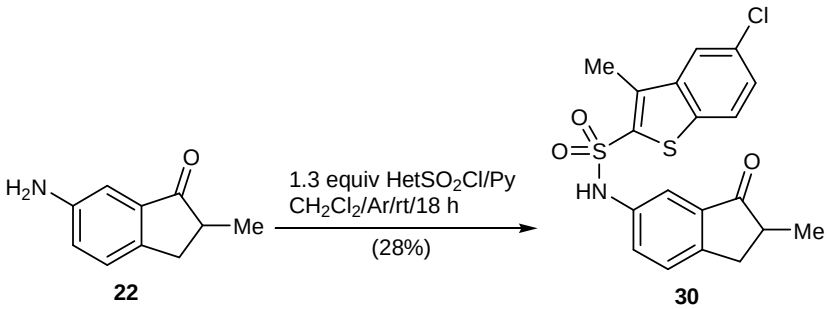

**29**

  - **Aldol-type condensation**

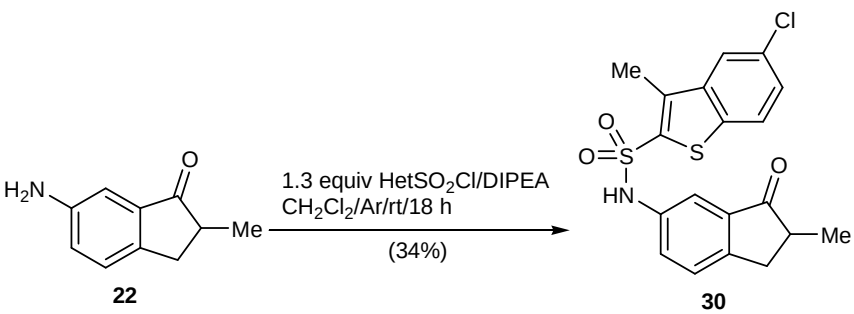



**29**

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

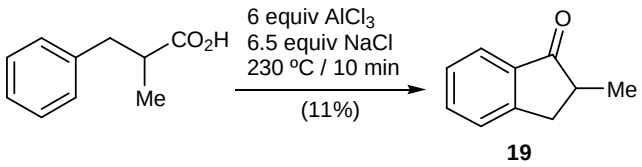



**22** **30**

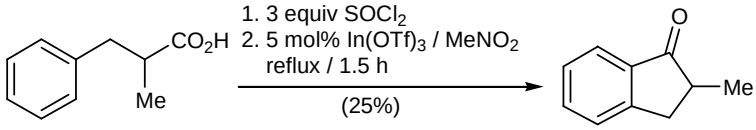



**22** **30**

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



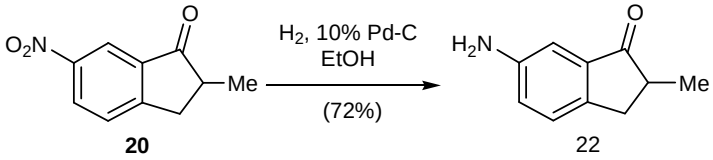

**19**



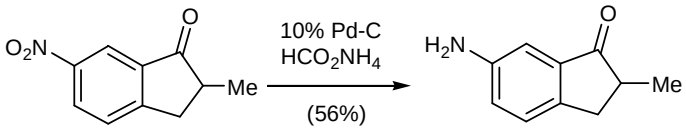

**19**

## ❖ ASSAYS RELATED WITH THE PREPARATION OF AMINOINDANONE 22

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



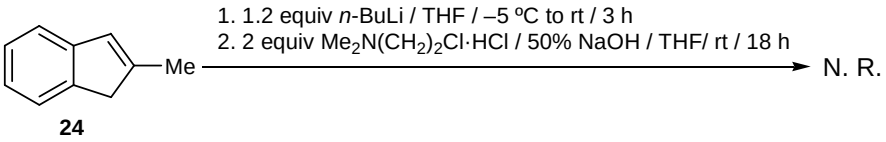

**20** 22



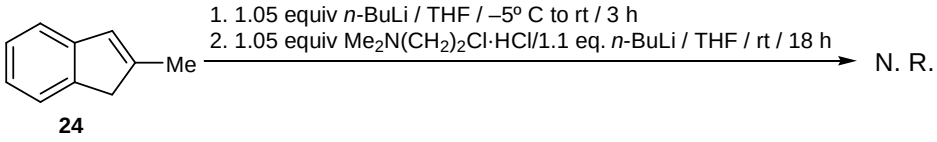

**20** **22**

## ❖ ASSAYS RELATED WITH THE PREPARATION OF INDENE 25

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




**24**




**24**

**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.

# Indene-Based Scaffolds. 2. An Indole−Indene Switch: Discovery of Novel Indenylsulfonamides as 5-HT$_6$ Serotonin Receptor Agonists[†]

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Scaffold selection involving an indole-to-indene core change led to the discovery of a series of indenylsulfonamides that act as 5-HT$_6$ serotonin receptor agonists. The variety of the targeted ligands and their synthetic complexity required multistep synthetic approaches. The novel indenylsulfonamides exhibited variable binding affinities for the 5-HT$_6$ receptor, and the in vitro primary binding profiles of the preferred compounds revealed them to be 5-HT$_6$ receptor agonists with $K_i$ values ≥4.5 nM. The structural changes responsible for enhancing the affinities indicated a directing effect modulated by the nature of the indene core, the substitution at the aminoethyl side chain, and especially by the aryl(heteroaryl)sulfonyl group on the indene 5-position. A representative of the family, the *N*-(inden-5-yl)imidazothiazole-5-sulfonamide (**43**), exhibited a high affinity and functioned as a potent full agonist for the 5-HT$_6$ receptor ($K_i$ = 4.5 nM, $EC_{50}$ = 0.9 nM, $E_{max}$ = 98%).

## Introduction

In the past few years, the 5-HT$_6$ serotonin receptor has become an attractive and promising therapeutic target for new potent and selective CNS agents with reduced peripheral side effects.[1−4] One of the most recent incorporations to the serotonin receptor family, the 5-HT$_6$ receptor was isolated from rat striatal mRNA in 1993 and the human 5-HT$_6$ receptor was identified subsequently.[5−7] It belongs to the G protein-coupled receptors (GPCRs), and its activation leads to an increase in cAMP production.[6,8] Although the function of this serotonin receptor subtype has not been fully elucidated, it is known to be located almost exclusively in the central nervous system, with high levels in the nucleus accumbens, cerebral cortex, and subfields of the hippocampus.[9,10] The pharmacology of the 5-HT$_6$ receptor has revealed significant differences compared with other serotonin receptor subtypes, revealing an affinity for certain tricyclic antipsychotic and antidepressant drugs. Consequently, the predominant distribution of the 5-HT$_6$ receptor population in the brain, combined with its high affinity for certain CNS drugs, has stimulated extensive research to discover new druggable targets and to elucidate a clearer picture of the role of the 5-HT$_6$ receptor in cognition and learning as well as certain types of neuropsychological and neuropsychiatric diseases such as affective and eating disorders, schizophrenia, and Alzheimer's disease.

An array of highly potent and selective 5-HT$_6$ ligands have been reported to date, the majority being identified as antagonists, whereas agonists have been far less explored.[2−4] A major drawback in agonist research appears to be their moderate selectivity, especially against different subtypes of 5-HT receptors. Early lead structures and pharmacological tools for the 5-HT$_6$ receptor are the antagonists **1** (Ro 04-6790),[11] **2** (SB-271046),[10,12] **3** (MS-245),[13,14] **4**,[13,14] and agonist **5** (EMTD).[13] A variety of indole-based ligands targeting 5-HT$_6$ receptors have been reported such as compounds **3**−**5** and the selective agonists **6** (WAY-181187)[15,16] and **7** (E-6837)[17−19] (see Figure 1). In an interesting study carried out concurrently with our work, Glennon and co-workers have examined the binding of several isotryptamines and indenes at 5-HT$_6$ recep-

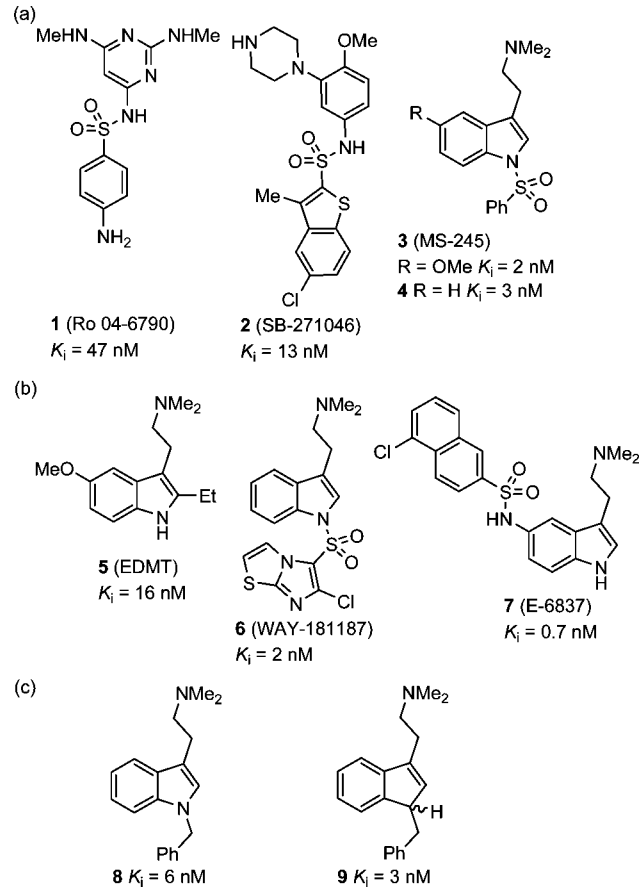


**Figure 1.** Several examples of 5-HT$_6$ serotonin receptor ligands: (a) antagonists **1**−**4**, (b) agonists **5**−**7**, (c) indole-indene compound pairs **8** and **9**.

[†] Part 1: ref 1.

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[§] ESTEVE.

10.1021/jm8009469 CCC: $40.75 
Published on Web 01/21/2009

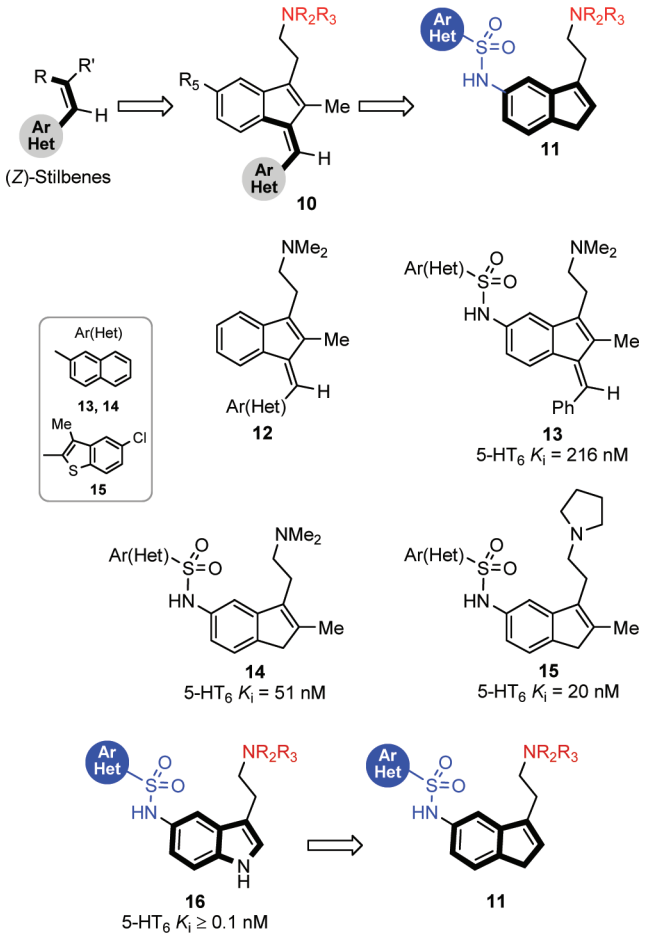


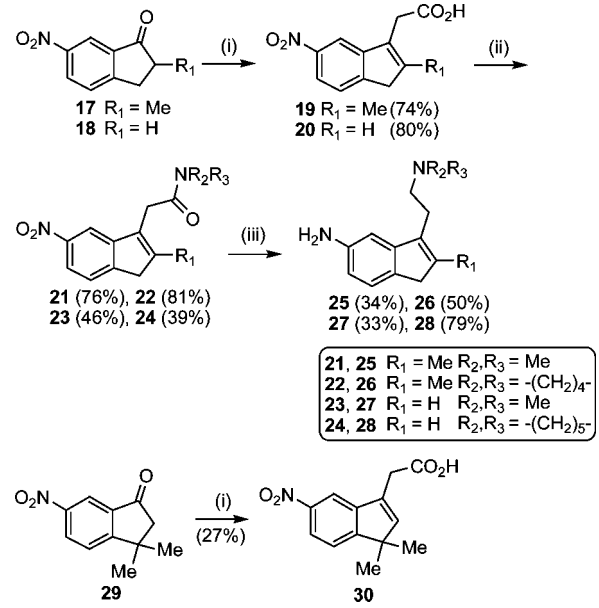

**Figure 2.** Design of 5-$HT_6$ serotonin receptor ligands: from (*Z*)-arylmethylideneindenes **10** to indenylsulfonamides **11**.

tors, and the high affinity of the compound pairs *N*-benzyltryptamine **8** ($K_i$ = 6 nM) and benzylindene **9** ($K_i$ = 3 nM) has revealed that the indolic nitrogen atom is not essential for binding.[20]

In the context of a project whose aim was to find (*Z*)-stilbenes with potential biological effects on the central nervous system (CNS), we began by applying a scaffold selection approach to an indene system such as the (*Z*)-arylmethylideneindenes **10**, in which the (*Z*)-stilbene moiety was embedded and with the classical *N*,*N*-dimethylaminoethyl CNS sidearm on the indene 3-position. The next selection step was the incorporation of a sulfonamide functionality on the indene 5-position in the *cis*-indene structure **10** and in the reduced indenylsulfonamides **11**. Several *cis*-indenes **12** were synthesized and profiled against a panel of radioligand binding assays, but none of them showed significant binding affinities whereas (*Z*)-benzylideneindenylsulfonamide **13** and the reduced counterparts **14** and**15** exhibited 5-$HT_6$ affinity with $K_i$ values ≥20 nM (Figure 2).[1] Among the variety of indole-based ligands targeting the 5-$HT_6$ receptors, we focused our attention on the potent and selective indolylsulfonamides **16** reported by Mercè et al. in 2003,[17] i.e., compound **7** (E-6837).[17−19]

We disclose our efforts in the discovery of novel indenylsulfonamides based on a scaffold selection of an indene system because, although indenes constitute a source of pharmacologically active molecules, their synthesis and pharmacology have not yet been extensively explored. Hence, an indole-to-indene core change from indolylsulfonamides **16** led to a series of indenylsulfonamides **11** with high affinity, showing $K_i$ values

**Scheme 1**[a]



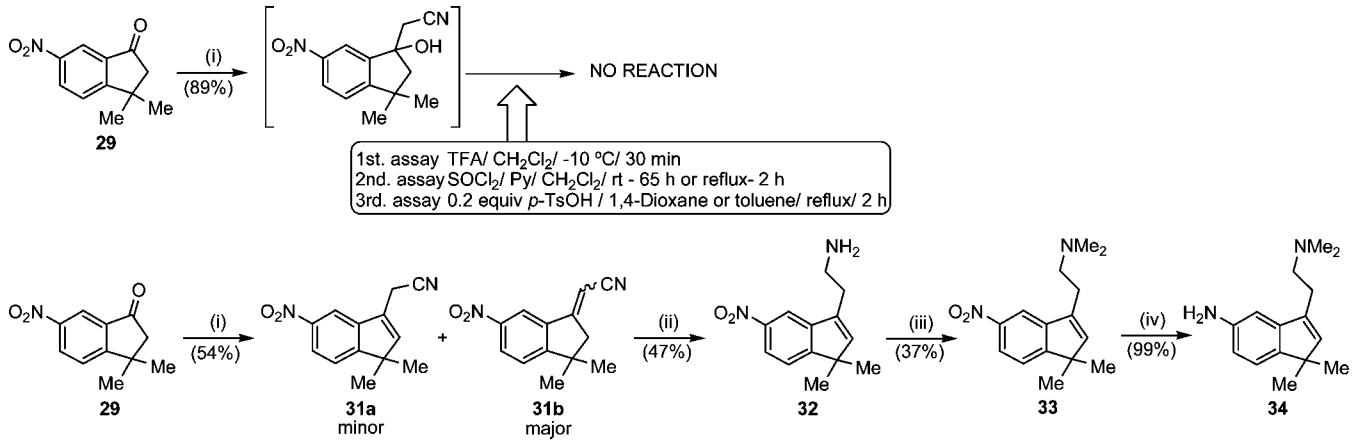

[a] Reagents and conditions: (i) (a) EtOAc, LHMDS, THF, −78 °C, (b) $H_2SO_4$, $H_2O$, 60 °C; (ii) (a) $SOCl_2$, $CH_2Cl_2$, reflux, (b) $Me_2NH$, pyrrolidine or piperidine, rt; (iii) (a) $AlH_3$−$NMe_2Et$, THF, 0 °C, (b) Zn, AcOH, rt.

≥4.5 nM and acting as 5-$HT_6$ receptor agonists. Notably, the scaffold was modified by satisfactorily replacing an indole (a $\pi$-excessive heteroaromatic ring) with an indene (a non aromatic carbocyclic system), passing from a structure of general type **16** with an unsubstituted pyrrolic $sp^2$ nitrogen atom on the indole 1-position to the designed indenylsulfonamides **11** bearing a $sp^3$ carbon atom instead (Figure 2).

Several parameters play a crucial role in a scaffold selection approach, a relevant one being the scaffold chemical tractability, referring to its synthetic accessibility and suitability for chemical modification.[21] Despite the utility of indenes in drug discovery and development, along with metallocene-based catalysis, their complexity means that synthetic approaches have been far less explored than in the case of heteroaromatic compounds such as indoles.[1,22,23] Among the possible synthetic approaches to indenylsulfonamides of general type **11**, a reasonable pathway appeared to involve inden-5-amines bearing a disubstituted *N*,*N*-aminoethyl moiety on the indene 3-position. We developed several processes to obtain the advanced key inden-5-amines as a consequence of the synthetic complexity and limitations of each set of compounds of the targeted ligands **11**.

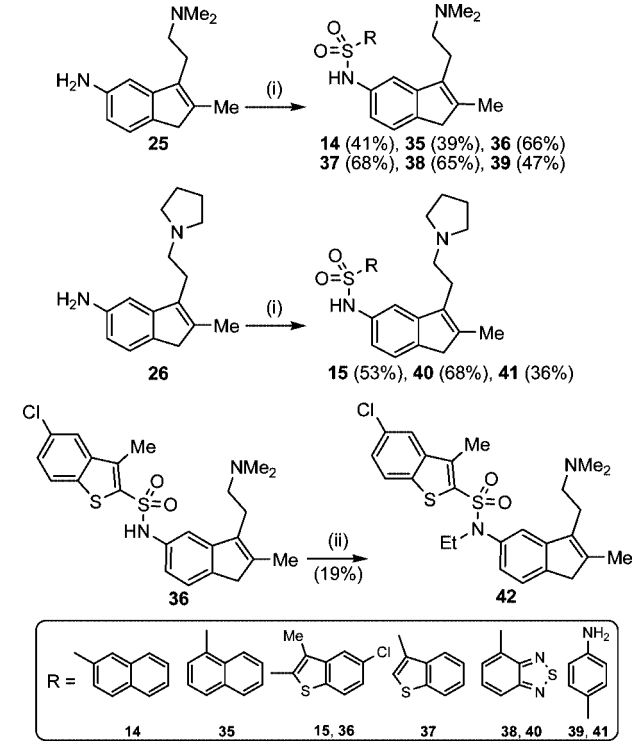
**Chemistry.** *N*-(Inden-5-yl)sulfonamides of general type **11** were synthesized following multistep procedures from suitable nitroindanones to the corresponding key inden-5-amines, which enabled us to diversify the synthesis of a variety of indenylsulfonamides **11** on the 5-position. As a starting point, the first protocol used for the preparation of the crucial inden-5-amines was a three-step sequence that began with the transformation of 6-nitroindanones **17**[1] or **18**[24] to (inden-3-yl)acetic acids **19** and **20** based on an aldol-type condensation as shown in Scheme 1. Reaction of indanones **17** or **18** with the lithium salt of ethyl acetate, followed immediately by dehydration and hydrolysis/isomerization, was examined and the best experimental protocol afforded the acetic acids **19** and **20** in good yield (>74%). These were then conveniently transformed to the corresponding acetamides **21**−**24** (see Supporting Information). Reduction of the amide group of **21**−**24** using $AlH_3$−$NMe_2Et$ was the crucial point of this synthetic route due to the troublesome quench process, which did not permit scale-up to more than 6 mmol.

**Scheme 2**[a]



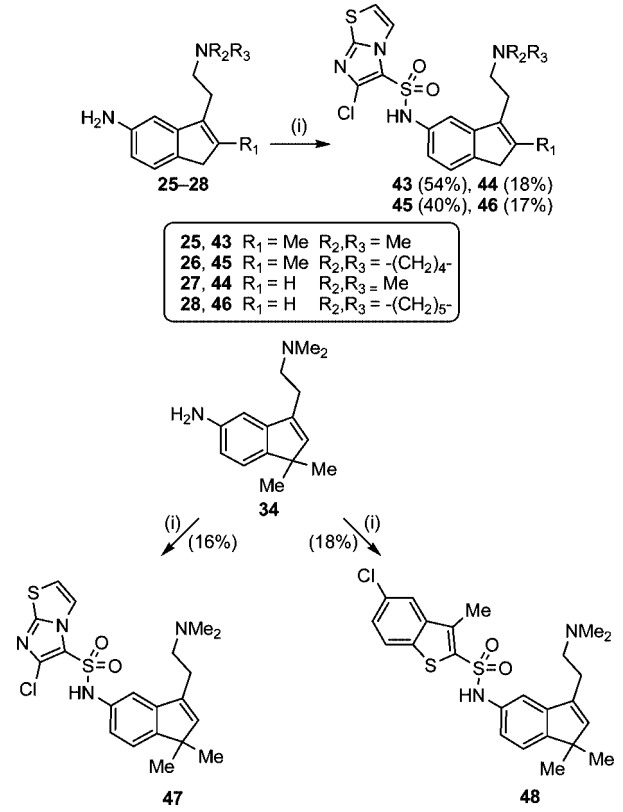

[a] Reagents and conditions: (i) (a) *n*-BuLi, MeCN, THF, −78 °C, (b) *p*-TsOH·$H_2O$, toluene, 150 °C; (ii) (a) $AlH_3$−$NMe_2Et$, THF, rt, (b) HCl, EtOH, 70 °C; (iii) HCOH, $NaBH_3CN$, AcOH, MeCN, rt; (iv) Zn, AcOH, rt.

**Scheme 3**[a]




[a] Reagents and conditions: (i) $RSO_2Cl$, pyridine, rt or (a) $RSO_2Cl$, pyridine, rt, (b) HCl, EtOH, reflux; (ii) (a) $K_2CO_3$, (b) EtI, dry MeCN, rt.

**Scheme 4**[a]




[a] Reagents and conditions: (i) $RSO_2Cl$, pyridine, rt.

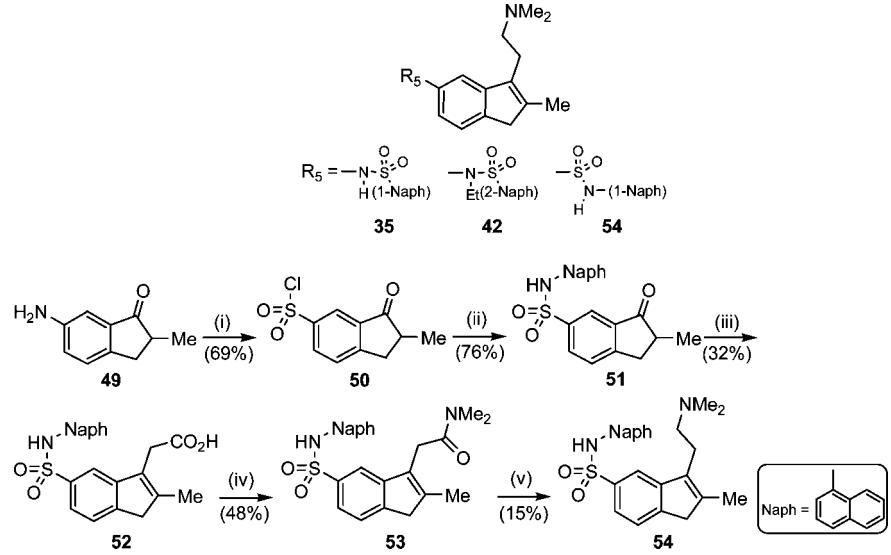
Then the nitro group was reduced with zinc in glacial acetic acid to afford the inden-5-amines **25**−**28**. Under the best reaction conditions and reagents, compounds **25**−**28** were prepared in 12−30% overall yields.

Following the same experimental procedure, transformation of 3,3-dimethyl-6-nitroindan-1-one **29**[25] to the acetic acid **30** proceeded in fairly low yield (Scheme 1). Alternatively, the aldol-type condensation was applied to nitroindanone **29** using the lithium salt of acetonitrile, and after experimenting with various reaction conditions and reagents, the condensation of **29** with the lithium salt of acetonitrile, followed immediately by dehydration, afforded an isomeric mixture of acetonitriles **31a** and **31b**, which were converted to the desired indenylethanamine **32**. Reductive *N*-dimethylation of **32** provided compound **33**, which was transformed with zinc in acetic acid to the key inden-5-amine **34** in 9% overall yield (see Scheme 2 and Supporting Information).

Reaction of 2-methylinden-5-amines **25** and **26** with the appropriate sulfonyl chloride afforded the *N*-(2-methylinden-5-yl)sulfonamides **14**, **15**, and **35**−**41** in acceptable yields (39% to 68%). Compounds **14** and **15** were also prepared by a specific protocol involving a five-step sequence.[1] Futhermore, *N*-alkylation of **36** provided *N*-ethyl-*N*-indenylsulfonamide **42** (Scheme 3).

The best reaction conditions for the preparation of indenylsulfonamides **14**, **15**, and **35**−**41** were then applied to the sulfonylation of 2-methylinden-5-amine **25** with 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride, providing *N*-(inden-5-yl)imidazothiazole-5-sulfonamide **43** in good yield (Scheme

**Scheme 5**[a]




[a] Reagents and conditions: (i) (a) $NaNO_2$, HCl, AcOH, MeCN, −10 °C, (b) $SO_2$, $CuCl_2 \cdot 2H_2O$, rt; (ii) 1-naphthylamine, pyridine, $CH_2Cl_2$, rt; (iii) (a) EtOAc, LHMDS, THF, −78 °C, (b) TFA, $CH_2Cl_2$, −5 °C, (c) NaOMe, MeOH, reflux; (iv) (a)$SOCl_2$, $CH_2Cl_2$, reflux, (b) $Me_2NH$, rt; (v) $AlH_3$−$NMe_2Et$, THF, 0 °C.

4). Using the same experimental protocol, inden-5-amines **26**−**28** were treated with the imidazothiazolesulfonyl chloride to afford *N*-(inden-5-yl)imidazothiazole-5-sulfonamides **44**−**46** with variable yields. Moreover, 1,1-dimethylinden-5-amine **34** was transformed to **47** and **48**.

It is noteworthy that Glennon and co-workers have examined the importance of the sulfonyl moiety for binding 5-$HT_6$ receptor ligands.[26] A logical extension of previously prepared indenylsulfonamides, e.g., **35** and **42**, was to examine the reversal of the sulfonamide linkage. We considered that a comparison with the model compound **54**, the reverse sulfonamide analogue of **35**, would allow us to examine the influence of the structural modification of the sulfonamide moiety on the binding of 5-$HT_6$ receptors (Scheme 5). Using the five-step sequence shown in Scheme 5, indenylsulfonamide **54** was prepared from aminoindanone **49**. A limiting factor of this protocol was that, although a variety of aromatic(heteroaromatic)sulfonyl chlorides are either commercially available or easily accessible, their related amines are difficult to obtain, as was the case for 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-amine, and so the commercial 1-naphthylamine was used instead. Thus, diazotization followed by chlorosulfonylation of aminoindanone **49** gave the sulfonyl chloride **50**, which led to indanone sulfonamide **51** upon reaction with 1-naphthylamine. Compound **51** was converted to indenylacetic acid **52**, which was transformed to acetamide **53**, followed by reduction with $AlH_3$−$NMe_2Et$ to give the reverse indenylsulfonamide **54**.

The structure of the new indenylsulfonamides was confirmed by spectroscopic methods. Their $^1H$ NMR and $^{13}C$ -NMR chemical shifts and physical data are gathered in the Experimental Section. Depending on the difficulties encountered in the isolation and purification, chromatographic separations were generally required and sometimes a second chromatographic run was necessary.

## Results and Discussion

The structural changes responsible for enhancing the 5-$HT_6$ receptor binding of the indenylsulfonamides of general type **11** were controlled by the synthetic accessibility of the targeted indene-based compounds. After analyzing different synthetic alternatives that could lead to indenylsulfonamides **11**, we chose a four-step route using inden-5-amines as the key intermediates and several sets of compounds **11** were conveniently synthesized. Compounds **14**, **15**, **35**, and **37**−**42** were tested in a radioligand competition binding assay at the 5-$HT_6$ receptor, showing affinities with $K_i$ values ≥20 nM (Table 1). Sulfonamide substitution of a 2-naphthyl nucleus in **14** was replaced by several aryl(heteroaryl) moieties, and the 5-chloro-3-methylbenzothiophene motif lowered the $K_i$ value to 20 nM for compound **15**. Nevertheless, application of Glennon's *p*-$NH_2$-phenyl theory[2] gave compound pairs **39** and **41** without and with discrete binding affinity, respectively. The inappreciable affinity shown by *N*-ethylsulfonamide analogue **42** allowed us to rule out additional studies with a *N*-alkylated sulfonamide group. In a similar manner to what had been observed with the indolylsulfonamide ligands **16**,[17,18] examination of the structure−activity relationships of compounds **14**, **15**, **35**, and **37**−**42** indicated a directing effect modulated by the nature of the aryl(heteroaryl) ring on the sulfonamide functionality.

Initial optimization identified compound **15** and the subsequent designing step was performed by changing the aryl(heteroaryl) group of the sulfonamide for a 3a-azapentalene motif and indenylsulfonamides **43**−**46** exhibited the best binding affinities at the 5-$HT_6$ receptors. Additional studies with compounds bearing a reversal of the sulfonamide linkage were discarded because compound **54** exhibited only moderate binding affinity (Table 1, see Experimental Section). Structural determinants for affinity enhancement within **43**−**47** showed that for the *N*,*N*-disubstituted aminoethyl functionality on the 3-position, the relative order was $Me_2N$− (**43**) ≈ $C_4H_8N$− (**45**) > $C_5H_{10}N$− (**46**), whereas for the indene substitution interrelations on the 1- and 2-positions, it was methylene (**43**−**46**) ≫ 1,1-dimethylmethylene (**47**) and $C_2$-Me (**43**) ≈ $C_2$−H (**44**), respectively (Figure 3). Notably, affinity activity was driven by the 6-chloroimidazo[2,1-*b*]thiazole structural motif and the preferred ligands were **43** ($K_i$ = 4.5 nM) and **44** ($K_i$ = 10 nM).

Selected indenylsulfonamides **14**, **15**, **37**, **41**, **43**−**46**, and the reverse indenylsulfonamide **54** were tested in a functional cAMP stimulation assay.[19] Compounds **14**, **37**, **43**, **44**, and **54** showed $E_{max}$ values ≥95%, and they functioned as 5-$HT_6$ receptor

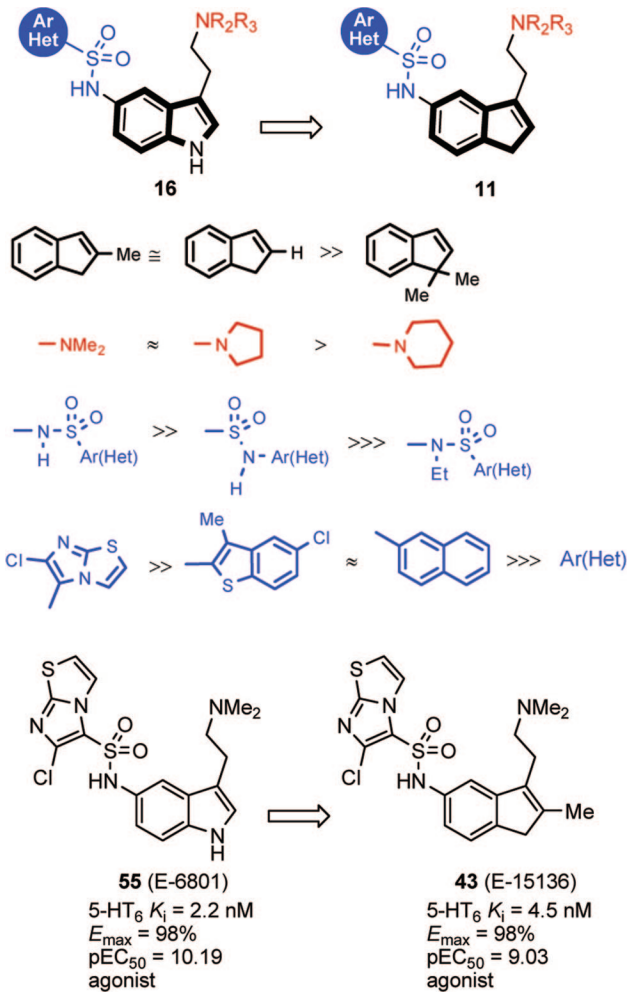



**Figure 3.** Indole-to-indene core change: from indolylsulfonamides **16** to indenylsulfonamides **11**.

agonists with $EC_{50}$ values ranging from 0.3 to 14 nM (Table 1, see Experimental Section). The indenylsulfonamides **43** and **44** displayed 5-$HT_6$ affinity and functionality comparable to the indole counterpart **55** (E-6801)[17,18,27,28] that has proved to be a potent and efficacious agonist at the wild-type and mutant 5-$HT_6$ receptors.[28] Compounds **43** and **44** profiled as full agonists with 0.9 and 0.3 nM of $EC_{50}$ values ($E_{max}$ of 98% and 99%), respectively. Further studies are underway with indenylsulfonamide **43**, which showed negligible activities against a panel of several serotoninergic and adrenergic receptors as well as the serotonin transporter (SERT) (see Table 2, see Experimental Section).

Indenylsulfonamide **43** appeared to be a suitable candidate for further studies because 5-$HT_6$ agonists are needed to remodel the current knowledge of the functional role and therapeutic relevance of 5-$HT_6$ receptors as well as to develop 5-$HT_6$ agents for the treatment of CNS-mediated diseases such as anxiety, depression, and other mental disorders. Moreover, 5-$HT_6$ receptor agonists have also been reported to be of interest for the treatment of disorders or diseases associated with food intake, including obesity, bulimia, and anorexia.

## Conclusions

The design of a series of indenylsulfonamides **11** based on a scaffold selection involving an indole-to-indene core change led to high-affinity 5-$HT_6$ serotonin receptor agonists. A synthetic multistep route for these ligands is reported using the inden-5-amines with a disubstituted *N*,*N*-aminoethyl group on the indene 3-position as the key intermediates. We determined a convenient route to these advanced inden-5-amines that involved a multistep sequence starting from 6-nitroindano-1-ones. Because of the variety of the targeted compounds **11** and their synthetic complexity, two synthetic protocols were efficiently used. The novel series of indenylsulfonamides **11** exhibited variable binding affinities for 5-$HT_6$ receptors, and the structural changes responsible for enhancing the affinities were modulated by: (i) the nature of the indene scaffold, (ii) the substitution at the aminoethyl side chain, and (iii) the nature of the aryl(heteroaryl)sulfonyl portion of the sulfonamide moiety. The indenylsulfonamides **43**−**46** bearing the 3a-azapentalene moiety displayed the best affinities because the 6-chloroimidazo[2,1-*b*]thiazole structural motif produced the most promising ligands **43** ($K_i$ = 4.5 nM) and **44** ($K_i$ = 10 nM) and continues to lead to compounds with high affinities at 5-$HT_6$ receptors. The functionality of five selected indenylsulfonamides **14**, **37**, **43**, **44**, and **54** proved to be potent agonists at 5-$HT_6$ receptors with $E_{max} \geq 95\%$ and with $EC_{50}$ values in the low-nanomolar or even subnanomolar range. These novel indenylsulfonamide 5-$HT_6$ agonists may be useful tools in elucidating the functional role and potential therapeutic uses of 5-$HT_6$ receptor ligands. In particular, *N*-(inden-5-yl)imidazothiazole-5-sulfonamide **43** warrants further pharmacological studies and more detailed in vivo research is in progress.

## Experimental Section

**General Methods.** The reaction yields were not optimized. Melting point: Gallenkamp melting point apparatus MPD350.BM2.5 with digital thermometer and are uncorrected. IR (KBr disks or thin film): Nicolet 205 FT or Perkin-Elmer 1430 spectrophotometers. $^1$H NMR: Varian Gemini 200 (200 MHz), Varian Gemini 300 (300 MHz), and Mercury 400 (400 MHz) spectrometers at 298 K. Chemical shifts were referenced and expressed in ppm ($\delta$) relative to the central peak of DMSO-$d_6$ (2.49 ppm) and TMS for chloroform-*d*. $^{13}$C NMR: Varian Gemini 200 (50.3 MHz), Varian Gemini 300 (75.4 MHz), and Mercury 400 (100.6 MHz) spectrometers at 298 K. Chemical shifts were referenced and expressed in ppm ($\delta$) relative to the central peak of DMSO-$d_6$ (39.7 ppm) and chloroform-*d* (77.0 ppm). MS were obtained using EI at 70 eV in a Hewlett-Packard spectrometer (HP-5989A model). Microanalyses were performed on a Carlo Erba 1106 analyzer. ESI-HRMS: Mass spectra were obtained using an Agilent LC/MSD-TOF spectrometer. For the targeted compounds, the chemical purity was determined by HPLC using the following conditions: Waters Alliance 2690 and 2695 (software Millenium 3.20) and Agilent 1100 (software Chemstation A.06.03) equipment with XBridge C18, 3.5 $\mu$, 0.46 cm × 10 cm column; acetonitrile (ACN)/10 mM ammonium bicarbonate mobile phase, gradient conditions: 0−12 min, from 5% ACN until 95% ACN; 12 − 17 min, isocratic 95% ACN; flow rate 1 mL/min; temperature 35 °C; $\lambda$ = 210 nm; $t_R$ = 5.4 min. TLC: Merck precoated silica gel 60 F254 plates using UV light (254 nm) as a visualizing agent and/or $H_2PtCl_2$ 3% aq/KI 10% aq (1:1) or $KMnO_4$ ethanolic solution. Column chromatography was performed on silica gel 60 ACC 35−70 $\mu$m Chromagel (SDS) or neutral alumina 90 activity II−III (Merck).

**Materials.** 2-Naphthalenesulfonyl chloride, 1-naphthalenesulfonyl chloride, and 5-chloro-3-methyl-1-benzothiophene-2-sulfonyl chloride, 1-benzothiophene-3-sulfonyl chloride, 2,1,3-benzothiadiazole-4-sulfonyl chloride, 4-acetamidobenzenesulfonyl chloride, 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride, and naphthalen-1-amine are commercial and used as received. 2-Methyl-6-nitroindan-1-one **17**,[1] 6-nitroindan-1-one**18**,[24] 3,3-dimethyl-6-nitroindan-1-one **29**,[25] and 6-amino-2-methylindan-1-one **49**[1] were prepared as previously described.

**Synthesis of (5-Nitroinden-3-yl)acetic Acids 19 and 20. General Procedure.** To a sufficient amount of dry THF cooled to −78 °C, a solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.1 equiv) was added in an argon atmosphere. Then dry EtOAc (1.05 equiv) was added and the resulting mixture was stirred at −78 °C for 30 min. Finally, a solution of 2-methyl-6-nitroindan-1-one **17** or 6-nitroindan-1-one**18** (1.0 equiv) in the sufficient amount of dry THF was added and the resulting mixture was kept at −78 °C for 1 h. The reaction mixture was acidified with 1N HCl, and the temperature was allowed to rise gradually until reaching room temperature and was extracted with EtOAc. The organic extracts were dried with anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. The previous residue was added to a 50% $H_2SO_4$ aqueous solution, cooled to −5 °C, and then was heated to 60 °C for 10 h. The reaction mixture was extracted with EtOAc, and the organic layer was washed with saturated $Na_2CO_3$ aqueous solution. The aqueous layer was neutralized with 5N HCl and extracted with EtOAc. The combined organic extracts, after being dried with anhydrous $Na_2SO_4$ and filtered, were evaporated to dryness. The residue obtained was used directly in the next step without further purification.

**(2-Methyl-5-nitro-1*H*-inden-3-yl)acetic Acid 19.** The above procedure was followed using dry EtOAc (2.20 mL, 22.5 mmol), LHMDS (1.0 M in THF, 24.0 mL, 24.0 mmol), and 2-methyl-6-nitroindan-1-one **17** (4.00 g, 20.9 mmol) in dry THF (110 mL) and 50% $H_2SO_4$ aq solution (60 mL). (3-Indenyl)acetic acid **19** (3.60 g, 74%) was obtained as an off-white solid; mp 208−10 °C. IR (KBr disk): $\nu$(COO-H) 3090; $\nu$(C═O) 1703; $\nu(NO_2)$ 1515, 1332 $cm^{-1}$. $^1H$ NMR (200 MHz, DMSO-$d_6$): $\delta$ 2.09 (s, 3H), 3.52 (s, 2H), 3.57 (s, 2H), 7.60 (d, $J$ = 8.4 Hz, 1H), 7.98−8.02 (m, 2H) ppm. $^{13}C$ NMR (DMSO-$d_6$, 50.3 MHz): $\delta$ 14.3 ($CH_3$), 31.0 ($CH_2$), 42.6 ($CH_2$), 113.0 (CH), 119.2 (CH), 123.9 (CH), 145.9, 146.9, 147.6, 149.8, 171, 180.7 (C═O) ppm. CI-MS: $m/z$ (%): 234 (100) $[M + H]^+$.

**(5-Nitro-1*H*-inden-3-yl)acetic Acid 20.** The above procedure was followed using dry EtOAc (1.20 mL, 11.8 mmol), LHMDS (1.0 M in THF, 12.4 mL, 12.4 mmol), and 6-nitroindan-1-one **18** (2.00 g, 11.3 mmol) in dry THF (35 mL) and 50% $H_2SO_4$ aq solution (100 mL). (3-Indenyl)acetic acid **20** (2.00 g, 80%) was obtained as an off-white solid; mp 195−6 °C. IR (KBr disk): $\nu$(COO-H) 3106; $\nu$(C═O) 1700; $\nu(NO_2)$ 1510, 1343 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ 3.71 (d, $J$ = 0.9 Hz, 2H), 3.83 (d, $J$ = 0.9 Hz, 2H), 6.82 (s,1H), 7.86 (dd, $J$ = 2.4, 8.1 Hz, 1H), 8.25 (dd, $J$ = 2.4, 8.1 Hz, 1H), 8.33 (d, $J$ = 2.1 Hz, 1H) ppm.$^{13}C$ NMR (DMSO-$d_6$, 50.3 MHz): $\delta$ 33.3 ($CH_2$), 37.9 ($CH_2$), 114.2 (CH), 119.9 (CH), 124.4 (CH), 135.3 (CH), 136.5, 145.9, 146.7, 151.4, 171.7 (C═O) ppm. EI-MS: $m/z$ (%): 219 (100) [$M^{+\bullet}$], 174 (81) [$M^{+\bullet}$ − 45], 128 (84) [$M^{+\bullet}$ − 91].

**Synthesis of Amide Derivatives 21−24. General Procedure.** The sufficient amount of $SOCl_2$ was added to a suspension of (3-indenyl)acetic acid **19** or **20** (1.0 equiv) in dry $CH_2Cl_2$. Then the reaction mixture was heated to reflux temperature until total dissolution. After the resulting solution had cooled down, the excess $SOCl_2$ was evaporated at reduced pressure. The residue obtained was dissolved in dry $CH_2Cl_2$, cooled to 0 °C, and dimethylamine, pyrrolidine, or piperidine (2.25−2.5 equiv) were added and the resulting solution was stirred at room temperature for 18 h. Water was added to the reaction mixture and extracted with EtOAc. The organic extracts, after being dried with anhydrous $Na_2SO_4$ and filtered, were evaporated to dryness. The residue obtained was purified by silica gel column chromatography (hexanes:EtOAc as eluent).

***N*,*N*-Dimethyl-2-(2-methyl-5-nitro-1*H*-inden-3-yl)acetamide 21.** The above procedure was followed using (3-indenyl)acetic acid **19** (3.90 g, 16.6 mmol), $SOCl_2$ (15 mL), and dimethylamine (40% in water, 4.75 mL, 37.4 mmol) in dry $CH_2Cl_2$ (150 mL). Acetamide derivative **21** was obtained as a yellow solid (3.28 g, 76%); mp 110−1 °C. IR (KBr disk): $\nu$(N−C═O) 1641; $\nu(NO_2)$ 1515, 1342 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.13 (s, 3H), 2.99 (s, 3H), 3.16 (s, 3H), 3.44 (s, 2H), 3.59 (s, 2H), 7.43 (d, $J$ = 8.8 Hz, 1H), 7.97−8.02 (m, 2H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 MHz): $\delta$ 14.4 ($CH_3$), 30.5 ($CH_2$), 35.7 ($CH_3$), 37.5 ($CH_3$), 42.9 ($CH_2$), 113.4 (CH), 119.3 (CH), 123.1 (CH), 130.5, 144.5, 147.4, 147.8, 149.1, 169.3 (C═O) ppm. EI-MS: $m/z$ (%): 260 (9) [$M^{+\bullet}$], 72 (100) [$M^{+\bullet}$ − 188].

**1-[(2-Methyl-5-nitro-1*H*-inden-3-yl)acetyl]pyrrolidine 22.** The above procedure was followed using (3-indenyl)acetic acid **19** (2.0 g, 8.58 mmol), $SOCl_2$ (4 mL), and pyrrolidine (1.80 mL, 21.4 mmol) in dry $CH_2Cl_2$ (130 mL). Pyrrolidine derivative **22** was obtained as a yellow solid (2.00 g, 81%); mp 128−9 °C. IR (KBr disk); $\nu$(N−C═O) 1624; $\nu(NO_2)$ 1513, 1336 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.86−2.07 (m, 4H), 2.14 (s, 3H), 3.44 (s, 2H), 3.47−3.61 (m, 6H), 7.43 (d, $J$ = 8.0 Hz, 1H), 7.97−8.06 (m, 2H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 MHz): $\delta$ 14.5 ($CH_3$), 24.4 ($CH_2$), 26.3 ($CH_2$), 31.8 ($CH_2$), 42.9 ($CH_2$), 46.0 ($CH_2$), 46.9 ($CH_2$), 113.5 (CH), 119.3 (CH), 123.1 (CH), 130.4, 144.5, 147.4, 147.8, 149.1, 167.7 (C═O) ppm. EI-MS: $m/z$ (%): 286 (42) [$M^{+\bullet}$], 269 (50) [$M^{+\bullet}$ − 17], 98 (100) [$M^{+\bullet}$ − 188].

***N*,*N*-Dimethyl-2-(5-nitro-1*H*-inden-3-yl)acetamide 23.** The above procedure was followed using (3-indenyl)acetic acid **20** (0.650 g, 2.94 mmol), $SOCl_2$ (2 mL), and dimethylamine (40% in water, 0.400 mL, 7.37 mmol) in dry $CH_2Cl_2$ (23 mL). Acetamide derivative **23** was obtained as an off-white solid (0.340 g, 46%); mp 93−4 °C. IR (KBr disk): $\nu$(N−C═O) 1641; $\nu(NO_2)$ 1512, 1345 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 3.03 (s, 3H), 3.11 (s, 3H), 3.50 (d, $J$ = 1.5, 2 Hz, 2H), 3.69 (d, $J$ = 1.5 Hz, 2H), 6.53 (s, 1H), 7.56 (d, $J$ = 8.4 Hz, 1H), 8.11 (dd, $J$ = 1.9, 8.2 Hz, 1H), 8.18 (d, $J$ = 2.1 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): $\delta$ 33.2 ($CH_3$), 35.6 ($CH_2$), 37.8 ($CH_2$), 38.2 ($CH_3$), 114.3 (CH), 120.3 (CH), 123.9 (CH), 133.8 (CH), 137.3 (C), 146.1 (C), 147.4 (C), 150.9 (C), 169.7 (C═O) ppm. EI-MS: $m/z$ (%): 246 (48) [$M^{+\bullet}$], 72 (100) [$M^{+\bullet}$ − 174].

**1-[(5-Nitro-1*H*-inden-3-yl)acetyl]piperidine 24.** The above procedure was followed using (3-indenyl)acetic acid **20** (0.550 g, 2.51 mmol), $SOCl_2$ (2 mL), and piperidine (0.600 mL, 6.27 mmol) in dry $CH_2Cl_2$ (23 mL). Acetamide derivative **24** was obtained as a greenish solid (0.280 g, 39%); mp 91−2 °C. IR (KBr disk): $\nu$(N−C═O) 1618; $\nu(NO_2)$ 1518, 1345 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.52−1.69 (m, 6H), 3.46 (t, $J$ = 5.4 Hz, 2H), 3.50−3.51 (m, 2H), 3.62 (d, $J$ = 5.4 Hz, 2H), 3.67−3.69 (m, 2H), 6.53 (t, $J$ = 1.8 Hz, 1H), 7.56 (dd, $J$ = 0.6, 8.4 Hz, 1H), 8.12 (dd, $J$ = 1.9, 8.1 Hz, 1H), 8.19 (d, $J$ = 2.1 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): $\delta$ 24.4 ($CH_2$), 25.5 ($CH_2$), 26.5 ($CH_2$), 33.2 ($CH_2$), 38.2 ($CH_2$), 42.9 ($CH_2$), 47.3 ($CH_2$), 114.3 (CH), 120.3 (CH), 123.9 (CH), 133.5 (CH), 137.7, 146.1, 147.5, 150.9, 167.7 (C═O) ppm. EI-MS: $m/z$ (%): 286 (53) [$M^{+\bullet}$], 112 (100) [$M^{+\bullet}$ − 174].

**Synthesis of Inden-5-amines 25−28. General Procedure.** To a sufficient amount of dry THF cooled to 0 °C, $AlH_3$−$NMe_2Et$ (0.5 M in toluene, 1.1 equiv) was added. Then a solution of amide derivatives **21**, **22**, **23**, or **24** (1.0 equiv) in dry THF cooled to 0 °C was added. At the end of the addition, the mixture was maintained at the same temperature in an argon atmosphere for 30 min. THF:$H_2O$ (1:1) was added slowly to the reaction mixture, the temperature was allowed to rise slowly to room temperature, was acidified with 1N HCl, and was extracted with EtOAc. The aqueous layer was basified with $Na_2CO_3$ and extracted with $CH_2Cl_2$. The combined organic extracts, after being dried with anhydrous $Na_2SO_4$ and filtered, were evaporated to dryness. To a solution of the previous residue in glacial AcOH, zinc (6.0−16 equiv) was added in portions. The resulting suspension was stirred at room temperature for 18 h. The reaction mixture was filtered through celite, and the filtered liquids were evaporated to dryness. The residue obtained was dissolved in $CH_2Cl_2$ and washed with 10% $NaHCO_3$ aqueous solution. The organic extract, after being dried with anhydrous $Na_2SO_4$ and filtered, was evaporated to dryness. The residue obtained was purified by silica gel column chromatography ($CH_2Cl_2$/$NH_3$:MeOH as eluent).

**3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-amine 25.** The above procedure was followed using acetamide derivative **21** (0.280 g, 1.08 mmol) and $AlH_3$−$NMe_2Et$ (0.5 M in toluene, 2.40 mL, 1.20 mmol) in dry THF (20 mL) and zinc (1.00 g, 15.3 mmol)

in glacial AcOH (20 mL). Inden-5-amine **25** (80.0 mg, 34%) was obtained as a brown solid; mp 68−9 °C. IR (thin film): $\nu(NH_2)$ 3343, 3209 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.05 (s, 3H), 2.33 (s, 6H), 2.40−2.45 (m, 2H), 2,61−2,69 (m, 2H), 3.18 (s, 2H), 6.46 (dd, $J$ = 2.2, 8.0 Hz, 1H), 6.62 (d, $J$ = 2.2 Hz, 1H), 7.12 (d, $J$ = 8.6 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 MHz): $\delta$ 14.1 ($CH_3$), 23.9 ($CH_2$), 41.1 ($CH_2$), 45.4 ($CH_3$), 58.3 ($CH_2$), 105.6 (CH), 110.7 (CH), 123.5 (CH), 132.7 (C), 134.4 (C), 140.4 (C), 144.9 (C), 147.6 ppm. CI-MS: $m/z$ (%): 247 (76) $[M + H]^+$, 58 (100) $[M - 188]^+$.

**2-Methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-amine 26.** The above procedure was followed using pyrrolidine derivative **22** (2.00 g, 7.00 mmol) and $AlH_3-NMe_2Et$ (0.5 M in toluene, 15.4 mL, 7.70 mmol) in dry THF (80 mL) and zinc (2.90 g, 44.3 mmol) in glacial AcOH (50 mL). Inden-5-amine **26** (0.850 g, 50%) was obtained as a brown solid; mp 74−5 °C. IR (KBr disk): $\nu(NH_2)$ 3440, 3306 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.80−1.87 (m, 4H), 2.04 (s, 3H), 2.52−2.78 (m, 8H), 3.17 (s, 2H), 3.68 (br s, 2H), 6.45 (dd, $J$ = 2.2, 8.0 Hz, 1H), 6.64 (d, $J$ = 2.2 Hz, 1H), 7.11 (d, $J$ = 8.0 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 MHz): $\delta$ 14.0 ($CH_3$), 23.5 ($CH_2$), 25.3 ($CH_2$), 41.9 ($CH_2$), 54.2 ($CH_2$), 55.1 ($CH_2$), 105.7 (CH), 110.7 (CH), 123.4 (CH), 132.7, 134.6, 140.4, 144.9, 147.6 ppm. EI-MS: $m/z$ (%): 242 (17) $[M^{+\bullet}]$, 84 (100) $[M^{+\bullet} - 158]$.

**3-[2-(Dimethylamino)ethyl]-1*H*-inden-5-amine 27.** The above procedure was followed using acetamide derivative **23** (0.650 g, 2.64 mmol) and $AlH_3-NMe_2Et$ (0.5 M in toluene, 5.81 mL, 2.90 mmol) in dry THF (25 mL) and zinc (1.40 g, 21.3 mmol) in glacial AcOH (10 mL). Inden-5-amine **27** (175 mg, 33%) was obtained as a brown oil. IR (thin film): $\nu(NH_2)$ 3336 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 2.33−2.35 (m, 6H), 2.60−2.64 (m, 2H), 2.66−2.71 (m, 2H), 3.22−3.23 (m, 2H), 6.22 (d, $J$ = 1.6 Hz, 1H), 6.55 (dd, $J$ = 2.0, 7.6 Hz, 1H), 6.73 (d, $J$ = 2.0 Hz, 1H), 7.2 (d, $J$ = 7.8 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 100.6 MHz): $\delta$ 26.0 ($CH_2$), 37.0 ($CH_2$), 45.3 ($CH_3$), 58.2 ($CH_2$), 106.2 (CH), 111.9 (CH), 124.0 (CH), 129.5 (CH), 134.5, 141.8, 144.9, 146.4 ppm. EI-MS: $m/z$ (%): 202 (2) $[M^{+\bullet}]$, 58 (100) $[M^{+\bullet} - 144]$.

**3-(2-Piperidin-1-ylethyl)-1*H*-inden-5-amine 28.** The above procedure was followed using piperidine derivative **24** (0.400 g, 1.40 mmol) and $AlH_3-NMe_2Et$ (0.5 M in toluene, 3.10 mL, 1.55 mmol) in dry THF (28 mL) and zinc (1.50 g, 22.4 mmol) in glacial AcOH (6 mL). Inden-5-amine **28** (0.270 g, 79%) was obtained as a brown oil. IR (thin film): $\nu(NH_2)$ 3340 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.62−1.67 (m, 6H), 2.51 (m, 4H), 2.66−2.70 (m, 4H), 3.23 (d, $J$ = 1.8 Hz, 1H), 6.21 (m, 1H), 6.55 (dd, $J$ = 2.3, 8.0 Hz, 1H), 6.75 (d, $J$ = 1.5 Hz, 1H), 7.21 (d, $J$ = 7.5 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): $\delta$ 24.4 ($CH_2$), 25.3 ($CH_2$), 25.9 ($CH_2$); 37.1 ($CH_2$), 54.6 ($CH_2$), 58.1 ($CH_2$), 106.3 (CH), 111.9 (CH), 124.0 (CH), 129.5 (CH), 134.6, 142.6, 144.9, 146.5 ppm.

**(1,1-Dimethyl-5-nitro-1*H*-inden-3-yl)acetic Acid 30.** To dry THF (2 mL) cooled to −78 °C, a solution of LHMDS (1.0 M in THF, 2.70 mL, 2.70 mmol) was added in an argon atmosphere. Then dry EtOAc (0.250 mL, 2.56 mmol) was added, and the resulting mixture was stirred at −78 °C for 30 min. Finally, a solution of 3,3-dimethyl-6-nitroindan-1-one **29** (0.500 g, 2.44 mmol) in THF (12 mL) and the resulting mixture was kept at −78 °C for 2 h. The reaction mixture was acidified with 1N HCl, the temperature was allowed to rise gradually until reaching room temperature, and was extracted with EtOAc (3 × 15 mL). The organic extracts were dried with anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. The previous residue was added to a 50% $H_2SO_4$ aqueous solution (15 mL), cooled to −5 °C, and was heated to 60 °C for 7.5 h. Water (40 mL) was added to the reaction mixture and was extracted with EtOAc (3 × 20 mL). The organic extracts, after being dried with anhydrous $Na_2SO_4$ and filtered, were evaporated to dryness. The residue obtained was crushed with dry $CH_2Cl_2$ and filtered to afford indenylacetic acid **30** (163 mg, 27%) as an off-white solid; mp 269−70 °C. IR (KBr disk): $\nu$(COO-H) 3090; $\nu$(C═O) 1682; $\nu(NO_2)$ 1630 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO): $\delta$ 1.28 (s, 6H), 3.12 (s, 2H), 6.62−6.63 (m, 1H), 7.68 (d, $J$ = 8.4 Hz, 1H), 8.24 (dd, $J$ = 2.0, 8.4 Hz, 1H), 8.58 (d, $J$ = 2.0 Hz, 1H) ppm. $^{13}C$ NMR (DMSO, 100.6 MHz): $\delta$ 29.2 ($CH_3$), 42.7, 47.5 ($CH_2$), 112.5 (CH), 117.2 (CH), 124.6 (CH), 125.8 (CH), 139.5, 147.6, 156.4, 163.6, 167.7 (C═O) ppm. EI-MS: $m/z$ (%): 247 (20) $[M^{+\bullet}]$, 230 (100) $[M^{+\bullet} - 17]$.

**(1,1-Dimethyl-5-nitro-1*H*-inden-3-yl)acetonitrile 31a and (3,3-Dimethyl-6-nitro-2,3-dihydro-1*H*-inden-1-ylidene)acetonitrile 31b.** To a stirred solution of *n*-BuLi (1.6 M in hexanes, 15.2 mL, 24.36 mmol) in dry THF (6 mL), at −78 °C under argon atmosphere, was added acetonitrile (1.10 mL, 21.45 mmol). After stirring for 1 h at −78 °C, a solution of 3,3-dimethyl-6-nitroindan-1-one **29** (2.00 g, 9.74 mmol) in dry THF (40 mL) was added and the resulting mixture was stirred at the same temperature for 2 h. The reaction mixture was poured into ice-1N HCl and extracted with EtOAc (3 × 300 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. To a solution of the previous residue in toluene (125 mL) was added *p*-TsOH·$H_2O$ (1.10 g, 5.57 mmol) and was refluxed for 2 h. The reaction mixture was diluted with EtOAc (125 mL) and washed with brine (2 × 125 mL). The organic extract was dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. Purification of the residue obtained by silica gel column chromatography (hexanes:EtOAc as eluent) afforded a mixture of isomeric nitriles **31a** and **31b** (1.20 g, 54%) as a brown solid; mp 101−2 °C. IR (KBr disk): $\nu$(CN) 2209; $\nu(NO_2)$ 1523, 1345 $cm^{-1}$. $^1H$ (300 MHz, $CDCl_3$): $\delta$ 1.38 (s, 18H), 2.89 (d, $J$ = 2.1 Hz, 2H), 3.06 (d, $J$ = 2.7 Hz, 2H), 3.61 (d, $J$ = 1.5 Hz, 2H), 5.49−5.51 (m, 1H), 5.83−5.84 (m, 1H), 6.64−6.66 (m, 1H), 7.44−7.49 (m, 3H), 8.05 (d, $J$ = 1.8 Hz, 1H), 8.19 (dd, $J$ = 2, 8.2 Hz, 1H), 8.28 (d, $J$ = 2.1 Hz, 1H), 8.30 (d, $J$ = 2.4 Hz, 1H), 8.33−8.34 (m, 1H), 9.10 (d, $J$ = 2.1 Hz, 1H) ppm. EI-MS $m/z$ (%): 228 (52) $[M^{+\bullet}]$, 213 (100) $[M^{+\bullet} - 15]$.

**2-(1,1-Dimethyl-5-nitro-1*H*-inden-3-yl)ethanamine 32.** On a sufficient amount of dry THF cooled to 0 °C, $AlH_3-NMe_2Et$ (0.5 M in toluene, 3.70 mL, 1.83 mmol) was added. Then, a solution of isomeric nitriles **31a** and**31b** (0.200 g, 0.920 mmol) in dry THF (7 mL) cooled to 0 °C was added. At the end of the addition, the mixture was stirred at room temperature in an argon atmosphere for 3 h. A solution of THF:$H_2O$ (1:1, 20 mL) was added slowly to the reaction mixture and extracted with EtOAc (3 × 25 mL). The organic extracts, after being dried with anhydrous $Na_2SO_4$ and filtered, were evaporated to dryness. A solution of the previous residue in 4N HCl/EtOH (10 mL) was stirred at 70 °C for 16 h. The reaction mixture was evaporated to dryness, dissolved in water, basified with saturated $Na_2CO_3$ aqueous solution, and extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered, and evaporated. Purification of the residue by silica gel column chromatography ($CH_2Cl_2/NH_3$: MeOH as eluent) afforded indenylethanamine **32** (100 mg, 47%) as a dark-red oil. IR (thin film): $\nu(NH_2)$ 3349, 3209; $\nu(NO_2)$ 1520, 1344 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.33 (s, 6H), 3.04 (t, $J$ = 7 Hz, 2H), 3.54 (t, $J$ = 6 Hz, 1H), 6.26 (s, 1H), 7.28−7.43 (m, 1H), 8.06−8.14 (m, 2H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 MHz): $\delta$ 24.3 ($CH_3$), 28.8 ($CH_2$), 29.2 (CH), 31.5, 48.7, 50.0 ($CH_2$), 114.3 (CH), 120.8 (CH), 121.3 (CH), 137.6, 144.7 (CH), 160.8 ppm. EI-MS: $m/z$ (%): 232 (10) $[M^{+\bullet}]$, 70 (100) $[M^{+\bullet} - 162]$.

**2-(1,1-Dimethyl-5-nitro-1*H*-inden-3-yl)-*N*,*N*-dimethylethanamine 33.** To a stirred solution of amine derivative **32** (0.400 g, 1.57 mmol) in acetonitrile (10 mL) was added 37% aqueous formaldehyde (1.26 mL, 45.6 mmol), $NaBH_3CN$ (0.500 g, 7.89 mmol), and glacial AcOH (0.2 mL). The reaction mixture was stirred at room temperature for 20 h, diluted with EtOAc (30 mL), and washed with 2N $Na_2CO_3$ (3 × 20 mL) and brine (20 mL). The organic extract, after being dried with anhydrous $Na_2SO_4$ and filtered, was evaporated to dryness. The residue obtained was purified by silica gel column chromatography ($CH_2Cl_2/NH_3$:MeOH as eluent) to afford 2-(inden-3-yl)ethanamine **33** (153 mg, 37%) as a brown oil. IR (thin film): $\nu(NO_2)$ 1521, 1344 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.34 (s, 6H), 2.83 (s, 6H), 2.93−3.01 (m, 2H), 3.22−3.31 (m, 2H), 6.32 (s, 1H), 7.45 (d, $J$ = 8.2 Hz, 1H), 8.08−8.16 (m, 2H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 MHz): $\delta$ 21.3 ($CH_2$), 24.0 ($CH_3$), 49.1, 61.3 ($CH_2$), 113.8 (CH), 121.3 (CH), 121.6 (CH), 134.2 (CH), 143.5, 144.9, 147.4, 160.4 ppm.

**3-[2-(Dimethylamino)ethyl]-1,1-dimethyl-1*H*-inden-5-amine 34.** To a solution of 2-(inden-3-yl)ethanamine **33** (110 mg, 0.420 mmol) in glacial AcOH (15 mL), zinc (0.700 g, 10.56 mmol) was added in portions. The resulting suspension was stirred at room temperature for 3 h. The reaction mixture was filtered through celite, and the filtered liquids were evaporated to dryness. The residue obtained was dissolved in $CH_2Cl_2$ (100 mL) and washed with 10% $NaHCO_3$ aqueous solution (3 × 50 mL). The organic extract, after being dried with anhydrous $Na_2SO_4$ and filtered and was evaporated to dryness to give inden-5-amine **34** (96.0 mg, 99%) as a brown oil. The product was used directly in the next step without further purification. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.24 (s, 6H), 2.74 (s, 6H), 2.80−2.86 (m, 2H), 3.10−3.19 (m, 2H), 6.08 (s, 1H), 6.54 (dd, $J$ = 1.8, 8.2 Hz, 1H), 6.67 (d, $J$ = 2.0 Hz, 1H), 7.05−7.08 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ 21.9 ($CH_2$), 24.8 ($CH_3$), 47.7, 50.2 ($CH_3$), 62.0($CH_2$), 106.1 (CH), 112.2 (CH), 121.6 (CH), 134.6, 142.9, 143.9, 143.9 (CH), 145.3 ppm.

**Synthesis of *N*-(Inden-5-yl)sulfonamides 14, 15, 35−41, 43−48. General Procedure.** To a stirred solution of inden-5-amine **25**, **26**, **27**, **28**, or **34** (1.0 equiv) in dry pyridine was added dropwise a solution of the corresponding sulfonyl chloride (1.0−1.5 equiv) in dry pyridine. The resulting mixture was stirred at room temperature (2−22 h). The reaction mixture was evaporated to dryness. The residue obtained was purified by silica gel column chromatography ($CH_2Cl_2$/$NH_3$:MeOH as eluent).

***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 14.** The above procedure was followed using inden-5-amine **25** (150 mg, 0.690 mmol) and 2-naphthalenesulfonyl chloride (173 mg, 0.760 mmol) in dry pyridine (10 mL). Indenylsulfonamide **14** (116 mg, 41%) was obtained as a yellow oil. The spectral data of **14** were identical to those previously reported.[1]

***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-1-sulfonamide 35.** The above procedure was followed using inden-5-amine **25** (100 mg, 0.460 mmol) and 1-naphthalenesulfonyl chloride (115 mg, 0.510 mmol) in dry pyridine (5 mL). Indenylsulfonamide **35** (73.0 mg, 39%) was obtained as an off-white solid; mp 200−1 °C. IR (KBr disk): $\nu$($SO_2$) 1320, 1158 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.98 (s, 3H), 2.18−2.23 (m, 2H), 2.26 (s, 6H), 2.45−2.52 (m, 2H), 3.11 (s, 2H), 6.70 (d, $J$ = 2.9 Hz, 1H), 6.86 (dd, $J$ = 2.0, 9.0 Hz, 1H), 7.09 (d, $J$ = 7.8 Hz, 1H), 7.40−7.46 (m, 1H), 7.53−7.58 (m, 1H), 7.63−7.69 (m, 1H), 7.87−7.90 (m, 1H), 7.98 (d, $J$ = 8.1 Hz, 1H), 8.21 (dd, $J$ = 1.4, 7.2 Hz, 1H), 8.75−8.87 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ 13.7 ($CH_3$), 23.2 ($CH_2$), 42.0 ($CH_2$), 44.8 ($CH_3$), 57.4 ($CH_2$), 111.1 (CH), 116.5 (CH), 123.3 (CH), 123.9 (CH), 124.5 (CH), 126.6 (CH), 128.0 (CH), 128.3, 128.8 (CH), 130.1 (CH), 133.6, 134.1 (CH), 134.6, 135.3, 138.7, 140.9, 147.0 ppm. ESI(+)-HRMS calcd for $C_{24}H_{27}N_2O_2S$ $[M + H]^+$, 407.1788; found, 407.1787.

**5-Chloro-*N*-{3-[2-(dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}-3-methyl-1-benzothiophene-2-sulfonamide 36.** The above procedure was followed using inden-5-amine **25** (0.500 g, 2.31 mmol) and 5-chloro-3-methyl-1-benzothiophene-2-sulfonyl chloride (0.700 g, 2.43 mmol) in dry pyridine (20 mL). Indenylsulfonamide **36** (0.700 g, 66%) was obtained as an off-white solid; mp 158−9 °C. IR (KBr disk): $\nu$(NH) 3079; $\nu$($SO_2$) 1337, 1157 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.01 (s, 3H), 2.31−2.40 (m, 11H), 2.56−2.64 (m, 2H), 3.18 (s, 2H), 6.92−6.99 (m, 2H), 7.18 (d, $J$ = 8.0 Hz, 1H), 7.36 (dd, $J$ = 2.0, 8.0 Hz, 1H), 7.62−7.67 (m, 2H), 8.64 (br s, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ 12.2 ($CH_3$), 14.0 ($CH_3$), 22.9 ($CH_2$), 42.2 ($CH_2$), 44.7 ($CH_3$), 57.5 ($CH_2$), 113.4 (CH), 119.0 (CH), 123.2 (CH), 123.5 (CH), 127.5 (CH), 131.2, 133.7, 134.4, 136.5, 137.5, 140.3, 140.5, 141.5, 147.3 ppm. CI-MS: $m/z$ (%): 461 (27) $[M + H]^+$, 58 (100) $[M - 403]^+$. Anal. ($C_{23}H_{25}ClN_2O_2S_2 \cdot 0.75H_2O$) C, H, N, S.

***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}-1-benzothiophene-3-sulfonamide 37.** The above procedure was followed using inden-5-amine **25** (50.0 mg, 0.230 mmol) and 1-benzothiophene-3-sulfonyl chloride (60.0 mg, 0.250 mmol) in dry pyridine (2.5 mL). Indenylsulfonamide **37** (65.0 mg, 68%) was obtained as an off-white solid; mp 196−7 °C. IR (KBr disk): $\nu$(NH) 3117; $\nu$($SO_2$) 1325, 1151 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.00 (s, 3H), 2.20−2.24 (m, 2H), 2.26 (s, 6H), 2.49−2.53 (m, 2H), 3.16 (s, 2H), 6.73 (d, $J$= 2 Hz, 1H), 6.97 (dd, $J$ = 2, 7.4 Hz, 1H), 7.16 (d, $J$ = 8 Hz, 1H), 7.38−7.47 (m, 2H), 7.81−7.83 (m, 1H), 8.12 (s, 1H); 8.22 (dd, $J$ = 0.8, 7.2 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 100.6 MHz): $\delta$ 13.8 ($CH_3$), 23.3 ($CH_2$), 42.0 ($CH_2$), 44.8 ($CH_3$), 57.4 ($CH_2$), 111.7 (CH), 117.2 (CH), 122.6 (CH), 123.2 (CH), 123.4 (CH), 125.3 (CH), 125.4 (CH), 133.1, 133.7, 134.8, 135.1, 139.2, 140.1, 141.0, 147.1 ppm. ESI(+)-HRMS calcd for $C_{22}H_{25}N_2O_2S_2$ $[M + H]^+$, 413.1352; found, 413.1352.

***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}benzo[1,2,5]thiadiazole-4-sulfonamide 38.** The above procedure was followed using inden-5-amine **25** (0.300 g, 1.39 mmol) and 2,1,3-benzothiadiazole-4-sulfonyl chloride (0.360 mg, 1.52 mmol) in dry pyridine (13 mL). Indenylsulfonamide **38** (0.370 g, 65%) was obtained as a yellow solid; mp 66−7 °C. IR (KBr disk): $\nu$($SO_2$) 1335, 1158 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.99 (s, 3H), 2.17−2.24 (m, 2H), 2.28 (s, 6H), 2.48−2.57 (m, 2H), 3.10 (s, 2H), 6.71 (dd, $J$ = 2.0, 7.8 Hz, 1H), 6.85 (d, $J$ = 1.4 Hz, 1H), 7.06 (d, $J$ = 8.0 Hz, 1H), 7.60 (dd, $J$ = 7.0, 8.0 Hz, 1H), 8.15 (dd, $J$ = 1.2, 4.4 Hz, 1H), 8.18−8.20 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ 14.0 ($CH_3$), 23.5 ($CH_2$), 42.1 ($CH_2$), 45.4 ($CH_3$), 58.1 ($CH_2$), 112.0 (CH), 117.2 (CH), 123.5 (CH), 126.5 (CH), 128.3 (CH), 130.9, 132.2 (CH), 134.4, 140.0, 141.3, 147.7, 149.2, 155.2 ppm. CI-MS: $m/z$ (%): 415 (43) $[M + H]^+$, 58 (100) $[M - 356]^+$. Anal. ($C_{20}H_{25}N_4O_2S_2 \cdot {}^1/_3H_2O$) C, H, N, S.

**4-Amino-*N*-{3-[2-(dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}benzenesulfonamide 39.** The above procedure was followed using inden-5-amine **25** (0.400 g, 1.85 mmol) and 4-acetamidobenzenesulfonyl chloride (0.650 g, 2.79 mmol) in dry pyridine (10 mL). To a solution of the previous residue obtained in EtOH was added 37% HCl aqueous solution and was refluxed for 5 h. The reaction mixture was evaporated to dryness, dissolved in $Na_2CO_3$ saturated aqueous solution, and extracted with $CH_2Cl_2$ (3 × 25 mL). The organic extracts was dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. Indenylsulfonamide **39** (0.320 g, 47%) was obtained as a yellow solid; mp 69−70 °C. IR (KBr disk): $\nu$($NH_2$) 3458; $\nu$(NH) 3374; $\nu$($SO_2$) 1315, 1149 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.04 (s, 3H), 2.33−2.40 (m, 8H), 2.57−2.66 (m, 2H), 3.19 (s, 2H), 4.08 (br s, 2H), 6.52−6.59 (m, 2H), 6.81 (dd, $J$ = 2.2, 8.0 Hz, 1H), 6.90 (d, $J$ = 2.0 Hz, 1H), 7.18 (d, $J$ = 8.0 Hz, 1H), 7.49−7.55 (m, 2H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ 14.0 ($CH_3$), 23.4 ($CH_2$), 42.1 ($CH_2$), 45.2 ($CH_3$), 57.9 ($CH_2$), 112.5 (CH), 113.7 (CH), 118.0 (CH), 123.4 (CH), 127.1, 129.3 (CH), 134.4, 135.3, 139.3, 140.9, 147.4, 150.6 ppm. CI-MS: $m/z$ (%): 372 (82) $[M + H]^+$, 58 (100) $[M - 313]^+$. Anal. ($C_{20}H_{25}N_3O_2S \cdot CH_3OH$) C, H, N, S.

**5-Chloro-3-methyl-*N*-[2-methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]-1-benzothiophene-2-sulfonamide 15.** The above procedure was followed using inden-5-amine **26** (200 mg, 0.820 mmol) and 5-chloro-3-methyl-1-benzothiophene-2-sulfonyl chloride (232 mg, 0.910 mmol) in dry pyridine (15 mL). Indenylsulfonamide **15** (0.210 g, 53%) was obtained as a brown solid. The spectral data of **15** were identical to those previously reported.[1]

***N*-[2-Methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]benzo[1,2,5]thiadiazole-4-sulfonamide 40.** The above procedure was followed using inden-5-amine **26** (0.100 g, 0.410 mmol) and 2,1,3-benzothiadiazole-4-sulfonyl chloride (0.110 mg, 0.450 mmol) in dry pyridine (4 mL). Indenylsulfonamide **40** (0.120 g, 68%) was obtained as a yellow solid; mp 71−2 °C. IR (KBr disk): $\nu$(NH) 3257; $\nu$($SO_2$) 1335, 1157 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.83−1.89 (m, 1H), 1.98 (s, 3H), 2.32−2.41 (m, 2H), 2.56−2.62 (m, 6H), 3.09 (s, 2H), 6.75 (dd, $J$ = 2.0, 8.0 Hz, 1H), 6.86 (d, $J$ = 1.8 Hz, 1H), 7.06 (d, $J$ = 7.6 Hz, 1H), 7.59 (dd, $J$ = 7.0, 8.0 Hz, 1H), 8.12−8.20 (m, 2H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ 14.0 ($CH_3$), 23.6 ($CH_2$), 25.1 ($CH_2$), 42.1 ($CH_2$), 54.3 ($CH_2$), 55.0 ($CH_2$), 112.0 (CH), 117.2 (CH), 123.5 (CH), 126.4 (CH), 128.2 (CH), 130.9, 132.2 (CH), 134.4, 134.5, 139.9, 141.3, 147.6, 149.1, 155.2 ppm. EI-MS: $m/z$ (%): 440 (2) $[M^{+\bullet}]$, 84 (100) $[M^{+\bullet} - 356]$. Anal. ($C_{22}H_{24}N_4O_2S_2 \cdot 1.5H_2O$) C, H, N, S.

**4-Amino-*N*-[2-methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]benzenesulfonamide 41.** The above procedure was followed using inden-5-amine **26** (0.100 g, 0.410 mmol) and 4-acetamidobenzenesulfonyl chloride (0.150 mg, 0.620 mmol) in dry pyridine (7 mL). To a solution of the previous residue obtained in EtOH was added 37% HCl aqueous solution and was then refluxed for 5 h. The reaction mixture was evaporated to dryness, dissolved in $Na_2CO_3$ saturated aqueous solution, and extracted with $CH_2Cl_2$(3 × 25 mL). The organic extracts was dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. Purification of the residue obtained by silica gel column chromatography ($CH_2Cl_2$/$NH_3$:MeOH as eluent) afforded indenylsulfonamide **41** (60.0 mg, 36%) as an off-white solid; mp 81−2 °C. IR (KBr disk): $\nu(NH_2)$ 3452, 3376; $\nu$(NH) 3245; $\nu(SO_2)$ 1315, 1150 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.80−1.87 (m, 4H), 2.04 (s, 3H), 2.17−2.71 (m, 8H), 3.19 (s, 2H), 4.07 (s, 2H), 6.52−6.59 (m, 2H), 6.81 (dd, $J$ = 2.2, 8.0 Hz, 1H), 6.92 (d, $J$ = 1.8 Hz, 1H), 7.18 (d, $J$ = 7.6 Hz, 1H), 7.48−7.55 (m, 2H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): $\delta$ 14.1 ($CH_3$), 23.6 ($CH_2$), 25.1 ($CH_2$), 42.2 ($CH_2$), 54.2 ($CH_2$), 55.0 ($CH_2$), 112.7 (CH), 113.9 (CH), 118.0 (CH), 123.5 (CH), 127.5, 129.5 (CH), 134.7, 135.3, 139.6, 141.0, 147.6, 150.6 ppm. CI-MS: $m/z$ (%): 398 (63) $[M + H]^+$, 84 (100) $[M - 313]^+$. Anal. ($C_{22}H_{27}N_3O_2S \cdot CH_3OH$) C, H, N, S.

**6-Chloro-*N*-{3-[2-(dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 43.** The above procedure was followed using inden-5-amine **25** (0.500 g, 2.31 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.600 mg, 2.31 mmol) in dry pyridine (13 mL). Indenylsulfonamide **43** (0.540 g, 54%) was obtained as an orange solid; mp 201−2 °C. IR (KBr disk): $\nu$(NH) 3117; $\nu(SO_2)$ 1343, 1136 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.03 (s, 3H), 2.26−2.33 (m, 8H), 2.54−2.62 (m, 2H), 3.18 (s, 2H), 6.84 (d, $J$ = 1.8 Hz, 1H), 6.95 (d, $J$ = 4.4 Hz, 1H), 7.04 (dd, $J$ = 1.8, 8.0 Hz, 1H), 7.19 (d, $J$ = 7.8 Hz, 1H), 7.82 (d, $J$ = 4.8 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): $\delta$ 13.8 ($CH_3$), 23.5 ($CH_2$), 42.1 ($CH_2$), 44.9 ($CH_3$), 57.4 ($CH_2$), 111.6 (CH), 113.7 (CH), 116.9 (CH), 120.3 (CH), 123.5 (CH), 130.3, 133.5, 134.4, 139.6, 141.2, 147.3, 158.5 ppm. ESI(+)-HRMS calcd for $C_{19}H_{22}N_4O_2S_2Cl$ $[M + H]^+$, 437.0867; found, 437.0865.

**6-Chloro-*N*-{3-[2-(dimethylamino)ethyl]-1*H*-inden-5-yl}imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 44.** The above procedure was followed using inden-5-amine **27** (0.150 g, 0.740 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.190 mg, 0.740 mmol) in dry pyridine (5 mL). Indenylsulfonamide **44** (55.0 mg, 18%) was obtained as a yellow solid; mp 193−4 °C. IR (KBr): $\nu$(NH) 3100; $\nu(SO_2)$ 1256, 1118 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.35 (s, 6H), 2.51−2.56 (m, 2H), 2.57−2.67 (m, 2H), 3.24 (s, 2H), 6.24 (s, 1H), 6.98 (d, $J$ = 4.8 Hz, 1H), 7.02 (d, $J$ = 2.1 Hz, 1H), 7.10 (dd, $J$ = 2.1, 8.1 Hz, 1H), 7.30−7.31 (m, 2H), 7.82 (d, $J$ = 4.5 Hz, 1H) ppm. $^{13}C$ NMR (DMSO, 100.6 MHz): $\delta$ 25.1 ($CH_2$), 37.1 ($CH_2$), 44.1 ($CH_3$), 57.4 ($CH_2$), 111.3 (CH), 116.9 (CH), 117.6 (CH), 118.7, 120.1 (CH), 124.3 (CH), 130.6 (CH), 136.1, 136.5, 140.1, 141.3, 145.9, 149.4 ppm. ESI(+)-HRMS calcd for $C_{18}H_{20}N_4O_2S_2Cl$ $[M + H]^+$, 423.0711; found, 423.0711.

**6-Chloro-*N*-[2-methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 45.** The above procedure was followed using inden-5-amine **26** (0.200 g, 0.820 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.230 g, 0.910 mmol) in dry pyridine (7.5 mL). Indenylsulfonamide **45** (0.15 g, 40%) was obtained as an off-white solid; mp 99−100 °C. IR (KBr disk): $\nu$(NH) 3112; $\nu(SO_2)$ 1244, 1118 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.88−1.91 (m, 4H), 2.02 (s, 3H), 2.59−2.72 (m, 8H), 3.18 (s, 2H), 6.84 (d, $J$ = 4.6 Hz, 1H), 6.96 (dd, $J$ = 2.0, 8.0 Hz, 1H), 7.10 (d, $J$ = 1.8 Hz, 1H), 7.17 (d, $J$ = 7.6 Hz, 1H), 7.82 (d, $J$ = 4.4 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 50.3 MHz): $\delta$ 14.1 ($CH_3$), 23.5 ($CH_2$), 24.2 ($CH_2$), 42.2 ($CH_2$), 53.9 ($CH_2$), 54.4 ($CH_2$), 113.3 (CH), 113.4 (CH), 118.4 (CH), 120.2, 120.8 (CH), 123.7 (CH), 133.5, 136.5, 136.9, 139.0, 141.5, 147.2, 148.9 ppm. CI-MS: $m/z$ (%): 463 (25) $[M + H]^+$, 159 (100) $[M - 303]^+$. Anal. ($C_{21}H_{23}ClN_4O_2S_2 \cdot 2.6.H_2O$) C, H, N, S.

**6-Chloro-*N*-[3-(2-piperidin-1-ylethyl)-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 46.** The above procedure was followed using inden-5-amine **28** (0.150 g, 0.620 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.160 g, 0.620 mmol) in dry pyridine (5 mL). Indenylsulfonamide **46** (48.0 mg, 17%) was obtained as a yellow solid; mp 222−3 °C. IR (KBr disk): $\nu$(NH) 3124; $\nu(SO_2)$ 1228, 1112 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.50 (m, 2H), 1.65−1.67 (m, 5H), 2.50−2.55 (m, 5H), 2.64 (m, 2H), 3.20−3.23 (m, 2H), 6.23 (s, 1H), 6.95 (d, $J$ = 4.8 Hz, 1H), 7.04 (d, $J$ = 2.1 Hz, 1H), 7.10 (dd, $J$ =2.1, 6.6 Hz, 1H), 7.81 (d, $J$ = 4.5 Hz, 1H) ppm. $^{13}C$ NMR (DMSO, 100.6 MHz): $\delta$ 25.0 ($CH_2$), 36.9 ($CH_2$), 53.5 ($CH_2$), 56.5 ($CH_2$), 111.1 (CH), 116.7 (CH), 117.4 (CH), 119.8 (CH), 124.0 (CH), 130.4 (CH), 135.6 (C), 136.4 (C), 140.0 (C), 141.0 (C), 145.6 (C), 149.4 (C) ppm. ESI(+)-HRMS calcd for $C_{21}H_{24}N_4O_2S_2Cl$ $[M + H]^+$, 463.1024; found, 463.1036.

**6-Chloro-*N*-{3-[2-(dimethylamino)ethyl]-1,1-dimethyl-1*H*-inden-5-yl}imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 47.** The above procedure was followed using inden-5-amine **34** (53.0 mg, 0.230 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (65.0 mg, 0.250 mmol) in dry pyridine (2.5 mL). Indenylsulfonamide **47** (17.0 mg, 16%) was obtained as a yellow oil. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.22 (s, 6H), 2.77(s, 6H), 2.80−2.85(m, 2H), 3.03−3.11(m, 2H), 6.13 (s, 1H), 6.96 (d, $J$ = 4.4 Hz, 1H), 7.03−7.08 (m, 2H), 7.15−7.19 (m, 1H), 7.77 (d, $J$ = 4.8 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): $\delta$ 22.1 ($CH_2$), 24.3 ($CH_3$), 48.5 (C), 50.6 ($CH_3$), 61.7 ($CH_2$), 114.0 (CH), 114.2 (CH), 118.2 (CH), 120.4 (CH), 120.6 (CH), 122.0 (CH), 133.9, 134.3, 138.0, 143.2, 144.9, 149.8, 152.1 ppm. Anal. ($C_{20}H_{23}ClN_4O_2S_2 \cdot H_2O$) C, H, N, S.

**5-Chloro-*N*-{3-[2-(dimethylamino)ethyl]-1,1-dimethyl-1*H*-inden-5-yl}-3-methyl-1-benzothiophene-2-sulfonamide 48.** The above procedure was followed using inden-5-amine **34** (43.0 mg, 0.190 mmol) and 5-chloro-3-methyl-1-benzothiophene-2-sulfonyl chloride (58.0 mg, 0.200 mmol) in dry pyridine (2.5 mL). Indenylsulfonamide **48** (16.0 mg, 18%) was obtained as a yellow oil. IR (KBr disk): $\nu$(NH) 3151; $\nu(SO_2)$ 1332, 1159 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 200 MHz ($CDCl_3$): 1.23 (s, 6H), 2.37 (s, 3H), 2.71 (s, 6H), 2.74−2.82 (m, 2H), 3.03−3.11 (m, 2H), 6.13 (s, 1H), 6.97 (dd, $J$ = 2.0, 7.8 Hz, 1H), 7.09 (d, $J$ = 1.8 Hz, 1H), 7.20 (d, $J$ = 2.8 Hz, 1H), 7.42 (dd, $J$ = 2.0, 8.6 Hz, 1H), 7.68−7.74 (m, 2H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): $\delta$ 12.2 ($CH_3$), 21.9 ($CH_2$), 24.4 ($CH_3$), 48.5, 50.35 ($CH_3$), 61.7 ($CH_2$), 113.8 (CH), 120.2 (CH), 121.9 (CH), 123.3 (CH), 123.8 (CH), 127.9 (CH), 131.5, 134.4, 136.1, 137.0, 137.7, 140.5, 143.2, 144.8 (CH), 151.9. Anal. ($C_{24}H_{27}ClN_2O_2S_2 \cdot H_2O$) C, H, N, S.

**5-Chloro-*N*-[3-(2-dimethylaminoethyl)-2-methyl-1*H*-inden-5-yl]-*N*-ethyl-3-methyl-1-benzothiophene-2-sulfonamide 42.** To a stirred solution of indenylsulfonamide **36** (0.100 g, 0.220 mmol) in dry acetonitrile (30 mL) was added $K_2CO_3$ (0.180 g, 1.30 mmol) and then was stirred at room temperature for 1 h. To the resulting suspension was added ethyl iodide (0.020 mL, 0.230 mmol) and then was stirred for 18 h at the same temperature. The reaction mixture was filtered, diluted with water (50 mL), and extracted with EtOAc (2 × 50 mL). The organic extracts were dried with anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. Purification of the residue obtained by silica gel column chromatography ($CH_2Cl_2$/$NH_3$:MeOH as eluent) afforded indenyl-*N*-ethylsulfonamide **42** (20.0 mg, 19%) as a yellow oil. IR (thin film): $\nu(SO_2)$ 1352, 1169 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.14 (t, $J$ = 6.9 Hz, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 2.14 (s, 6H), 2.17−2.23 (m, 2H), 3.27 (s, 2H), 3.79 (q, $J$ = 6.9 Hz, 2H), 6.89−6.93 (m, 2H), 7.29 (dd, $J$ = 0.9, 9.0 Hz, 1H), 7.42 (dd, $J$ = 1.8, 9.0 Hz, 1H), 7.67 (dd, $J$ = 0.6, 3.0 Hz, 1H), 7.73−7.76 (m, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): 12.3 ($CH_3$), 14.1 ($CH_3$), 14.4 ($CH_3$), 23.9 ($CH_2$), 42.5 ($CH_2$), 45.3 ($CH_3$), 46.7 ($CH_2$), 58.1 ($CH_2$), 118.3 (CH), 123.4 (CH), 123.6 (CH), 123.7(CH), 125.0 (CH), 127.7 (CH), 131.4, 134.6, 136.4, 136.5, 137.7, 140.8, 141.2, 142.8, 147.7 ppm. CI-MS: $m/z$ (%): 489 (44) $[M + H]^+$, 58 (100) $[M - 430]^+$. Anal. ($C_{25}H_{29}ClN_2O_2S_2 \cdot H_2O$) C, H, N, S.

**2-Methyl-3-oxoindane-5-sulfonyl Chloride 50.** 6-Amino-2-methylindan-1-one **49**(1.00 g, 6.20 mmol) was dissolved in acetonitrile (50 mL) and after cooling to −10 °C, glacial AcOH (5 mL) and 37% HCl aqueous solution (2.5 mL) were added. To the mixture was added a solution of $NaNO_2$ (0.510 g, 7.44 mmol) in water (2 mL). After stirring at −10 °C for 30 min, $SO_2$ gas was bubbled in over 20 min and the, a solution of $CuCl_2 \cdot 2H_2O$ (1.30 g, 7.75 mmol) in water (2 mL) was added dropwise. The mixture was allowed to warm and stir for 18 h at room temperature. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL). The organic layer was washed with saturated $NaHCO_3$ aqueous solution (3 × 50 mL), dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness to give sulfonyl chloride **50** (1.0 g, 69%) as a yellow oil. The product was used directly in the next step without further purification. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.37 (d, $J$ = 7.2 Hz, 3H), 2.78−2.98 (m, 2H), 3.46−3.62 (m, 1H), 7.72 (d, $J$ = 8.2 Hz, 1H), 8.23 (dd, $J$ = 1.8, 8.0 Hz, 1H), 8.41 (d, $J$ = 1.4 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ 16.0 ($CH_3$), 35.3 ($CH_2$), 42.5 (CH), 123.1 (CH), 128.2 (CH), 131.9 (CH), 143.9 (C), 155.7 (C), 159.8 (C), 206.5 (C═O) ppm. EI-MS: $m/z$ (%): 244 (61) [$M^{+\bullet}$], 243 (100) [$M^{+\bullet}$ − 1], 229 (80) [$M^{+\bullet}$ − 15], 145 (66) [$M^{+\bullet}$ − 99], 115 (80) [$M^{+\bullet}$ − 129].

**2-Methyl-*N*-naphth-1-yl-3-oxoindane-5-sulfonamide 51.** To a stirred solution of naphthalen-1-amine (0.680 g, 4.72 mmol) and pyridine (2 mL) in dry $CH_2Cl_2$ (75 mL) was added a solution of sulfonyl chloride **50** (1.00 g, 4.29 mmol) in dry $CH_2Cl_2$ (20 mL) under argon atmosphere. After stirring at room temperature for 18 h, the reaction mixture was washed with 2.5N HCl (3 × 75 mL), dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. Purification of the residue obtained by silica gel column chromatography ($CH_2Cl_2$:MeOH as eluent) afforded indanone sulfonamide **51** (1.15 g, 76%) as a foamy solid; mp 133−4 °C. IR (KBr disk): $\nu$(NH) 3274; $\nu$(C═O) 1703; $\nu$($SO_2$) 1350, 1159 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.29 (d, $J$ = 7.4 Hz, 3H), 2.66−2.77 (m, 2H), 3.34−3.48 (m, 1H), 6.96 (br s, 1H), 7.37−7.47 (m, 5H), 7.71−7.86 (m, 4H), 8.20 (d, $J$ = 1.0 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ 16.0 ($CH_3$), 35.0 ($CH_2$), 42.4 (CH), 121.7 (CH), 123.0 (CH), 123.3 (CH), 125.4 (CH), 126.2 (CH), 126.5 (CH), 126.6 (CH), 127.6 (CH), 128.3 (CH), 129.0, 131.1, 132.9 (CH), 134.1, 136.7, 139.3, 157.7, 208.1 (C═O) ppm. EI-MS: $m/z$ (%): 351 (10) [$M^{+\bullet}$], 142 (100) [$M^{+\bullet}$ − 209].

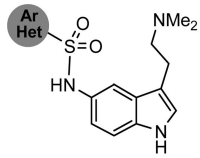
**{2-Methyl-5-[(1-naphthylamino)sulfonyl]-1*H*-inden-3-yl}acetic acid 52.** Dry EtOAc (0.300 mL, 2.87 mmol) was added dropwise to a stirred solution of LHMDS (1.0 M in THF, 5.80 mL, 5.80 mmol) in dry THF (3 mL) at −78 °C under argon atmosphere. After 15 min, a solution of indanone sulfonamide **51** (0.960 g, 2.73 mmol) in dry THF (16 mL) was added dropwise and the mixture was stirred for 1 h at the same temperature. The reaction mixture was acidified with 1N HCl and then was warmed to ambient temperature. The aqueous layer was separated and extracted with EtOAc (3 × 25 mL). The combined organic layers were evaporated to dryness. Trifluoroacetic acid (1.30 mL, 16.7 mmol) was added dropwise to a stirred solution of the resulting residue in dry $CH_2Cl_2$ (18 mL) at −5 °C. After 30 min, the mixture was concentrated in vacuo. To a stirred solution of the resultant residue in dry MeOH (18 mL) at room temperature was added a solution of sodium (0.3 g, 12.05 mmol) in dry MeOH (15 mL) under argon atmosphere. The resulting mixture was refluxed for 18 h. To cooled reaction mixture was added dropwise EtOH (30 mL) and was evaporated to dryness. The resulting residue was dissolved in water (100 mL) and was acidified with 5N HCl. The precipitate was filtered to give indenylacetic acid **52** (0.340 g, 32%) as an orange foamy solid; mp 119−20 °C. IR (KBr disk): $\nu$(NH) 3251; $\nu$(COO-H) 3251; $\nu$(C═O) 1710; $\nu$($SO_2$) 1311, 1151 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.05 (s, 3H), 3.21 (s, 2H), 3.49 (s, 2H), 7.15−7.32 (m, 4H), 7.38 (dd, $J$ = 1.8, 9.0 Hz, 1H), 7.52−7.57 (m, 2H), 7.64−7.68 (m, 1H), 7.76 (d, $J$ = 1.5 Hz, 1H), 7.85−7.88 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ 14.6 ($CH_3$), 31.1 ($CH_2$), 43.0 ($CH_2$), 117.3 (CH), 122.2 (CH), 123.2 (CH), 123.5 (CH), 123.8 (CH), 125.6 (CH), 126.5 (CH), 126.8 (CH), 127.4 (CH), 128.4(CH), 129.2, 129.5, 131.8, 134.4, 137.6, 145.5, 147.0, 147.6, 175.9 (C═O) ppm. EI-MS: $m/z$ (%): 393 (29) [$M^{+\bullet}$], 142 (100) [$M^{+\bullet}$ − 251].

***N*,*N*-Dimethyl-2-{2-methyl-5-[(1-naphthylamino)sulfonyl]-1*H*-inden-3-yl}acetamide 53.** The sufficient amount of $SOCl_2$ was added to a solution of indenylacetic acid **52** (0.280 g, 0.710 mmol) in dry $CH_2Cl_2$ (10 mL). Then the reaction mixture was heated to reflux temperature for 2 h. After the reaction mixture had cooled down, the excess $SOCl_2$ was evaporated at reduced pressure. The residue obtained was dissolved in dry $CH_2Cl_2$ (5 mL), cooled to 0 °C, and dimethylamine (40% in water, 0.220 mL, 1.78 mmol) was added, and the resulting solution was stirred at room temperature for 18 h. The reaction mixture was diluted with water (50 mL), acidified with 5N HCl, and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic extracts, after being dried with anhydrous $Na_2SO_4$ and filtered, were evaporated to dryness. The residue obtained was purified by silica gel column chromatography ($CH_2Cl_2$: MeOH as eluent) to afford acetamide derivative **53** (0.140 g, 48%) as a yellow foamy solid; mp 90−1 °C. IR (KBr disk): $\nu$(NH) 3056; $\nu$(C═O) 1630; $\nu$($SO_2$) 1314, 1151 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.02 (s, 3H), 2.91 (s, 3H), 2.99 (s, 3H), 3.20 (s, 2H), 3.45 (s, 2H), 7.17−7.32 (m, 4H), 7.35−7.44 (m, 3H), 7.63−7.67 (m, 1H), 7.74−7.79 (m, 1H), 7.98−8.02 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ 14.3 ($CH_3$), 30.6 ($CH_2$), 35.8 ($CH_3$), 37.5 ($CH_3$), 42.7 ($CH_2$), 117.0 (CH), 122.3 (CH), 122.8 (CH), 122.9 (CH), 123.1 (CH), 125.3 (CH), 126.1 (CH), 126.4 (CH), 126.9 (CH), 128.0 (CH), 129.4, 130.2, 131.8, 134.1, 137.3, 143.8, 147.1, 169.6 (C═O) ppm. EI-MS: $m/z$ (%): 420 (6) [$M^{+\bullet}$], 72 (100) [$M^{+\bullet}$ − 348].

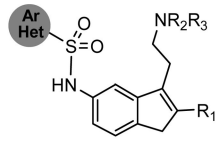
**3-[2-(Dimethylamino)ethyl]-2-methyl-*N*-naphth-1-yl-1*H*-indene-5-sulfonamide 54.** On a sufficient amount of dry THF cooled to 0 °C, $AlH_3$−$NMe_2Et$ (0.5 M in toluene, 0.600 mL, 0.300 mmol) was added. Then a solution of acetamide derivative **53** (70.0 mg, 0.170 mmol) in dry THF (5 mL) cooled to 0 °C was added. At the end of the addition, the mixture was maintained at the same temperature in an argon atmosphere for 30 min. A solution of THF:$H_2O$ (1:1, 10 mL) was added slowly to the reaction mixture, the temperature was allowed to rise slowly to room temperature, was basified with a 20% $NH_3$ aqueous solution, and was extracted with EtOAc (3 × 25 mL). The organic extracts, after being dried with anhydrous $Na_2SO_4$ and filtered, were evaporated to dryness. Purification of the residue obtained by silica gel column chromatography ($CH_2Cl_2$/$NH_3$:MeOH as eluent) gave indenesulfonamide **54** (11.0 mg, 15%) as a yellow oil. IR (thin film): $\nu$(NH) 3021; $\nu$($SO_2$) 1316, 1151 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 200 MHz ($CDCl_3$): $\delta$ 2.05 (s, 3H), 2.33−2.40 (m, 8H), 2.59−2.67 (m, 2H), 3.26 (s, 2H), 7.29−7.46 (m, 5H), 7.55−7.93 (m, 5H) ppm. $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ 14.1 ($CH_3$), 23.2 ($CH_2$), 42.6 ($CH_2$), 44.9 ($CH_3$), 57.6 ($CH_2$), 116.7 (CH), 121.7 (CH), 122.8 (CH), 123.0 (CH), 123.2 (CH), 125.4 (CH), 126.2 (CH), 126.5 (CH), 127.1 (CH), 128.3 (CH), 129.1, 131.8, 134.0, 134.2, 137.5, 142.2, 147.1, 147.6 ppm. EI-MS: $m/z$ (%): 406 (1) [$M^{+\bullet}$], 58 (100) [$M^{+\bullet}$ − 348]. ESI(+)-HRMS calcd for $C_{24}H_{27}N_2O_2S$ [M + H]$^+$, 407.1788; found, 407.1803.

**5-HT$_6$ Binding Assay.** Membranes from HEK-293 with human 5-HT$_6$ receptor expressed were supplied by Receptor Biology. The binding assays were performed as described by Roth et al.[29] with slight modifications. The radioligand used was [$^3$H]-LSD at 2.7 nM, and the final volume was 200 $\mu$L. The incubation was initiated by addition of 100 $\mu$L of membrane (22.9 $\mu$g of protein), and the incubation time was 60 min at 37 °C. After incubation, the membranes were collected onto polyethylenimine-pretreated glass fiber filters (Schleicher & Schnell 3362). The filters were washed with buffer (50 mM Tris Cl, pH = 7.4). Then filter sections were transferred to vials, and liquid scintillation cocktail was added to each vial. Nonspecific binding was determined with 100 $\mu$M serotonin. Competition binding data were analyzed by using the LIGAND program,[30] and assays were performed in triplicate determinations for each point. A linear regression line of data points is plotted, from which the concentration of competing ligand which displaces 50% of the specific binding of the radioligand ($IC_{50}$ value) is determined and the $K_i$ value is determined based upon the Cheng−Prusoff

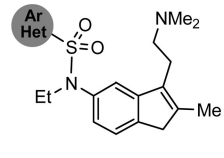
**Table 1.** 5-HT$_6$ Receptor Affinity and Functionality of Compounds **7**, **14**, **15**, **35**, **37**−**48**, **54**, and **55**



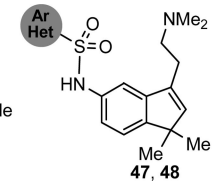

**7**, **55**



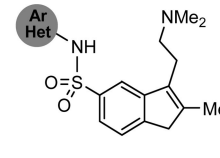

**14**, **15**, **35**, **37**–**41**, **43**–**46**



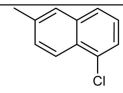
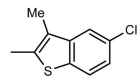
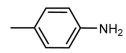
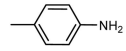
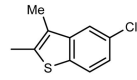
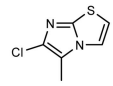
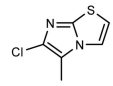
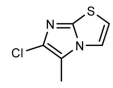
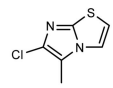
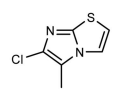
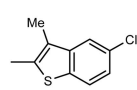
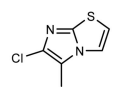

**42**




**47**, **48**

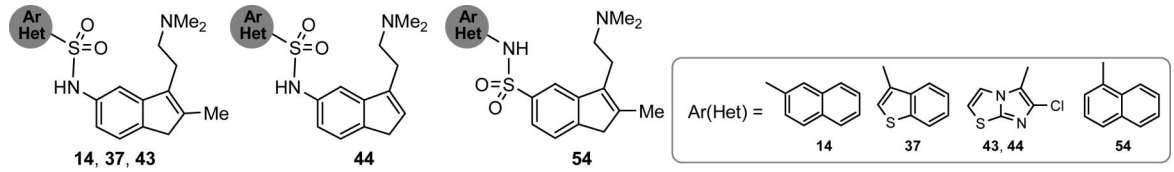



**54**

| Cpd. | $R_1$ | $NR_2R_3$ | Ar(Het) | % Inhib. @ 100 nM | $K_i$ (nM)[a] | $E_{max}$ (%)[b] | $EC_{50}$ (nM)[b] |
|---|---|---|---|---|---|---|---|
| **7**[c] | – | $NMe_2$ |  | | 0.7 | 96 | d |
| **14**[e] | Me | $NMe_2$ | 2-Naphthyl | 71 | 51 | 98 | 3.2 |
| **15**[e] | Me |  |  | f | 20 | 78 | |
| **35** | Me | $NMe_2$ | 1-Naphthyl | 78 | 276 | | |
| **37** | Me | $NMe_2$ |  | 88 | 53 | 101 | 0.3 |
| **38** | Me | $NMe_2$ |  | 16 | | | |
| **39** | Me | $NMe_2$ |  | 4 | | | |
| **40** | Me |  |  | 19 | | | |
| **41** | Me |  |  | 63 | | | |
| **42** | Me | $NMe_2$ |  | 3 | | | |
| **43** | Me | $NMe_2$ |  | g | 4.5 | 98 | 0.9 |
| **44** | H | $NMe_2$ |  | 87 | 10 | 99 | 0.3 |
| **45** | Me |  |  | 81 | 17 | 37 | |
| **46** | H |  |  | 81 | 31 | –58 | |
| **47** | H | $NMe_2$ |  | 24 | | | |
| **48** | H | $NMe_2$ |  | 2 | | | |
| **54** | Me | $NMe_2$ | 1-Naphthyl | 51 | | 95 | 14 |
| **55**[h] | – | $NMe_2$ |  | | 2.2 | 98 | i |

[a] The 5-HT$_6$ binding assay was performed in triplicate. [b] Agonism was expressed as $E_{max}$ and $EC_{50}$ values. [c] See refs 17−19. [d] $pEC_{50} = 9.53$. [e] See ref 1. [f] % Inhib @ 1 $\mu$M = 100. [g] % Inhib @ 1 $\mu$M = 97. [h] See refs 17, 18, and 28. [i] $pEC_{50} = 10.19$.

**Table 2.** Selectivity over Several Receptors and Serotonin Transporter (SERT) of Compounds **14**, **37**, **43**, **44**, and **54**




| compd | $\alpha_1$-adrenoceptor[a] $IC_{50}$ (nM) | $\alpha_{2A}$-adrenoceptor[b] $IC_{50}$ (nM) | 5-$HT_{1A}$[b] $IC_{50}$ (nM) | 5-$HT_{2C}$[b] $IC_{50}$ (nM) | SERT[c] $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| **14** | | >1000 | >1000 | | |
| **37** | | 700 | 1142 | | |
| **43** | >10000 | >1000 | >1000 | 1127 | >10000 |
| **44** | >10000 | >1000 | >1000 | >1000 | >10000 |
| **54** | | 1097 | >1000 | | |

[a] Rat receptor. [b] Human receptor. [c] Human transporter.

equation: $K_i = IC_{50}/(1 + L/K_D)$, where $L$ is the concentration of free radioligand used in the assay and $K_D$ is the dissociation constant of the radioligand for the receptor.

**Adenylyl Cyclase Activity Assay.** Functional effects of the compounds were evaluated by cAMP measurements on HEK-293F cells stably expressing the human 5-$HT_6$ receptor using a homogeneous time-resolved fluorescent (HTRF) assay format. After overnight serum-free medium incubation, cell suspensión (20000 cells per well) was added in 96-well culture plate in incubation buffer composed of Ham's F12 medium plus 1 mM 3-isobutyl-1-methyl-xanthine (IBMX) and 20 $\mu$M pargyline. Then 40 $\mu$L of cell suspension and 10 $\mu$L of either compound or vehicle were added to each well at indicated concentrations for 30 min at 37 °C in either the absence or presence (in antagonist experiments) of 5-HT. The reaction was stopped with 25 $\mu$L of cryptate and 25 $\mu$L of cross-linked allophycocyanin (XL-665). Plates were incubated for 1 h at room temperature and read at 665 nm/620 nm using a RubyStar plate reader (BMG LabTech).[19,27,28]

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**Supporting Information Available:** Assays related with the preparation of compounds **25**−**28** and **34** and NMR, HRMS spectra, and analytical data of targeted compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Alcalde, E.; Mesquida, N.; Frigola, J.; López-Pérez, S.; Mercè, R. Indene-based scaffolds. Design and synthesis of novel serotonin 5-$HT_6$ receptor ligands. *Org. Biomol. Chem.* **2008**, *6*, 3795–3810.

(2) (a) Glennon, R. A. Higher-End serotonin receptors: 5-$HT_5$, 5-$HT_6$, and 5-$HT_7$. *J. Med. Chem.* **2003**, *46*, 2795–2812. (b) Glennon, R. A.; Dukat, M. Serotonin Receptors and Drugs Affecting Serotonergic Neurotransmission. In *In Foye's Principles of Medicinal Chemistry*, 6th ed.; Lemke, T. L., Williams, D. A., Eds.; Lippincott, Williams & Wilkins: Philadelphia, 2008; pp 417−443.

(3) (a) Woolley, M. L.; Marsden, C. A.; Fone, K. C. 5-$HT_6$ receptors. *Curr. Drug Targets: CNS Neurol. Disord.* **2004**, *3*, 59–79. (b) Vickers, S. P.; Dourish, C. T. Serotonin receptor ligands and the treatment of obesity. *Curr. Opin. Invest. Drugs* **2004**, *5*, 377–88. (c) Nichols, D. E.; Nichols, C. D. Serotonin Receptors. *Chem. Rev.* **2008**, *108*, 1614–1641.

(4) Heal, D. J.; Smith, S. L.; Fisas, A.; Codony, X.; Buschmann, H. Selective 5-$HT_6$ receptor ligands: progress in the development of a novel pharmacological approach to the treatment of obesity and related metabolic disorders. *Pharmacol. Ther.* **2008**, *117*, 207–231.

(5) Monsma, F. J., Jr.; Shen, Y.; Ward, R. P.; Hamblin, M. W.; Sibley, D. R. Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol. Pharmacol.* **1993**, *43*, 320–327.

(6) Ruat, M.; Traiffort, E.; Arrang, J. M.; Tardivel-Lacombe, J.; Diaz, J.; Leurs, R.; Schwartz, J. C. A novel rat serotonin (5-$HT_6$) receptor: molecular cloning, localization and stimulation of cAMP accumulation. *Biochem. Biophys. Res. Commun.* **1993**, *193*, 268–276.

(7) Kohen, R.; Metcalf, M. A.; Khan, N.; Druck, T.; Huebner, K.; Lachowicz, J. E.; Meltzer, H. Y.; Sibley, D. R.; Roth, B. L.; Hamblin, M. W. Cloning, characterization, and chromosomal localization of a human 5-$HT_6$ serotonin receptor. *J. Neurochem.* **1996**, *66*, 47–56.

(8) Sebben, M.; Ansanay, H.; Bockaert, J.; Dumuis, A. 5-$HT_6$ receptors positively coupled to adenylyl cyclase in striatal neurones in culture. *NeuroReport* **1994**, *5*, 2553–2557.

(9) Sleight, A. J.; Boess, F. G.; Bos, M.; Bourson, A. The putative 5-$HT_6$ receptor: Localization and function. *Ann. N.Y. Acad. Sci.* **1998**, *861*, 91–96.

(10) Dawson, L. A.; Nguyen, H. Q.; Li, P. The 5-$HT_6$ receptor antagonist SB-271046 selectively enhances excitatory neurotransmission in the rat frontal cortex and hippocampus. *Neuropsychopharmacology* **2001**, *25*, 662–668.

(11) Sleight, A. J.; Boess, F. G.; Bos, M.; Levet-Trafit, B.; Riemer, C.; Bourson, A. Characterization of Ro 04-6790 and Ro 63-0563: potent and selective antagonists at human and rat 5-$HT_6$ receptors. *Br. J. Pharmacol.* **1998**, *124*, 556–562.

(12) Bromidge, S. M.; Brown, A. M.; Clarke, S. E.; Dodgson, K.; Gager, T.; Grassam, H. L.; Jeffrey, P. M.; Joiner, G. F.; King, F. D.; Middlemiss, D. N.; Moss, S. F.; Newman, H.; Riley, G.; Routledge, C.; Wyman, P. 5-Chloro-*N*-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulfon-amide (SB-271046): a potent, selective, and orally bioavailable 5-$HT_6$ receptor antagonist. *J. Med. Chem.* **1999**, *42*, 202–205.

(13) Glennon, R. A.; Lee, M.; Rangisetty, J. B.; Dukat, M.; Roth, B. L.; Savage, J. E.; McBride, A.; Rauser, L.; Hufesien, S.; Lee, D. K. H. 2-Substituted tryptamines: agents with selectivity for 5-$HT_6$ serotonin receptors. *J. Med. Chem.* **2000**, *43*, 1011–1018.

(14) Tsai, Y.; Dukat, M.; Slassi, A.; MacLean, N.; Demchyshyn, L.; Savage, J. E.; Roth, B. L.; Hufesein, S.; Lee, M.; Glennon, R. A. $N_1$-(Benzenesulfonyl)tryptamines as novel 5-$HT_6$ antagonists. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2295–2299.

(15) Cole, D. C.; Stock, J. R.; Lennox, W. J.; Bernotas, R. C.; Ellingboe, J. W.; Boikess, S.; Coupet, J.; Smith, D. L.; Leung, L.; Zhang, G.-M.; Feng, X.; Kelly, M. F.; Galante, R.; Huang, P.; Dawson, L. A.; Marquis, K.; Rosenzweig-Lipson, S.; Beyer, C. E.; Schechter, L. E. Discovery of $N_1$-(6-Chloroimidazo[2,1-*b*][1,3]-thiazole-5-sulfonyl-)tryptamine as a potent, selective, and orally active 5-$HT_6$ receptor agonist. *J. Med. Chem.* **2007**, *50*, 5535–5538.

(16) Schechter, L. E.; Lin, Q.; Smith, D. L.; Zhang, G.; Shan, Q.; Platt, B.; Brandt, M. R.; Dawson, L. A.; Cole, D.; Bernotas, R.; Robichaud, A.; Rosenzweig-Lipson, S.; Beyer, C. E. Neuropharmacological profile of novel and selective 5-$HT_6$ receptor agonists: WAY-181187 and WAY-208466. *Neuropsychopharmacology* **2007**, 1−13.

(17) Mercè, R. ; Andaluz, B.; Frigola, J. Sulphonamide derivatives, their preparation thereof and the application of same as medicaments. World Patent WO 03/042175 A1, CAN 138:401602, 2003.

(18) Holenz, J.; Mercè, R.; Díaz, J. L.; Guitart, X.; Codony, X.; Dordal, A.; Romero, G.; Torrens, A.; Mas, J.; Andaluz, B.; Hernández, S.; Monroy, X.; Sánchez, E.; Hernández, E.; Pérez, R.; Cubí, R.; Sanfeliu, O.; Buschmann, H. Medicinal chemistry driven approaches toward novel and selective serotonin 5-$HT_6$ receptor ligands. *J. Med. Chem.* **2005**, *48*, 1781–1795.

(19) Fisas, A.; Codony, X.; Romero, G.; Dordal, A.; Giraldo, J.; Mercè, R.; Holenz, J.; Heal, D.; Buschmann, H.; Pauwels, P. J. Chronic 5-$HT_6$ receptor modulation by E-6837 induces hypophagia and sustained

weight loss in diet-induced obese rats. *Br. J. Pharmacol.* **2006**, *148*, 973–983.

(20) Kolanos, R.; Siripurapu, U.; Pullagurla, M.; Riaz, M.; Setola, V.; Roth, B. L.; Dukat, M.; Glennon, R. A. Binding of isotryptamines and indenes at *h*5-$HT_6$ serotonin receptors. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1987–1991.

(21) Zhao, H. Scaffold selection and scaffold hopping in lead generation: a medicinal chemistry perspective. *Drug Discovery Today* **2007**, *12*, 149–155.

(22) Frigola, J.; Mercè, R.; Holenz, J.; Alcalde, E.; Mesquida, N.; López-Pérez, S. Preparation of indene derivatives for treatment of 5-$HT_6$ receptors mediated diseases. World Patent WO 07/054257 A2, **2007**. CAN 146:521555.

(23) (a) Tsukamoto, H.; Ueno, T.; Kondo, Y. Palladium(0)-catalyzed regioselective and multicomponent synthesis of 1,2,3-trisubstituted 1*H*-indenes. *Org. Lett.* **2007**, *9*, 3033–3036. (b) Ivchenko, P. V.; Nifant'ev, I. E.; Luzikov, Y. N.; Mkoyan, S. G. Unexpected reactivity of 3-(phenylethynyl)-1*H*-indenes towards nucleophiles: noncatalytic addition to triple bond with or without double bond migration. *Synthesis*, **2007**, 1038−1046.

(24) Musso, D. L.; Cochran, F. R.; Kelley, J. L.; McLean, E. W.; Selph, J. L.; Rigdon, G. C.; Orr, G. F.; Davis, R. G.; Cooper, B. R.; Styles, V. L.; Thompson, J. B.; Hall, W. R. Indanylidenes. 1. Design and synthesis of (*E*)-2-(4,6-Difluoro-1-indanylidene)acetamide, a potent, centrally acting muscle relaxant with antiinflammatory and analgesic activity. *J. Med. Chem.* **2003**, *46*, 399–408.

(25) Koelsch, C. F.; Leclaire, C. D. The reactions and enolization of cyclic diketones. V. (1) Some carbonyl reactions. *J. Org. Chem.* **1941**, *6*, 516–533.

(26) Sikazwe, D.; Bondarev, M. L.; Dukat, M.; Rangisetty, J. B.; Roth, B. L.; Glennon, R. A. Binding of sulfonyl-containing arylalkylamines at human 5-$HT_6$ serotonin receptors. *J. Med. Chem.* **2006**, *49*, 5217–5225.

(27) Romero, G.; Sánchez, E.; Pujol, M.; Pérez, P.; Codony, X.; Holenz, J.; Buschmann, H.; Pauwels, P. J. Efficacy of selective 5-$HT_6$ receptor ligands determined by monitoring 5-$HT_6$ receptor-mediated cAMP signaling pathways. *Br. J. Pharmacol.* **2006**, *148*, 1133–1143.

(28) Romero, G.; Pujol, M.; Pérez, P.; Buschmann, H.; Pauwels, P. J. Whole spectrum analysis of ligand efficacy at constitutively active human wild-type and S267K 5-$HT_6$ receptors in HEK-293F cells. *J. Pharmacol. Toxicol. Methods* **2007**, *55*, 144–150.

(29) Roth, B. L.; Craigo, S. C.; Choudhary, M. S.; Uluer, A.; Monsma, F. J., Jr.; Shen, Y.; Meltzer, H. Y.; Sibley, D. R. Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 1403–1410.

(30) Munson, P. J.; Rodbard, D. LIGAND: A versatile, computerized approach for characterization of ligand-binding systems. *Anal. Biochem.* **1980**, *107*, 220–239.

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# Supporting Information

## An Indole−Indene Switch: Discovery of Novel Indenylsulfonamides as 5-$HT_6$ Receptor Agonists

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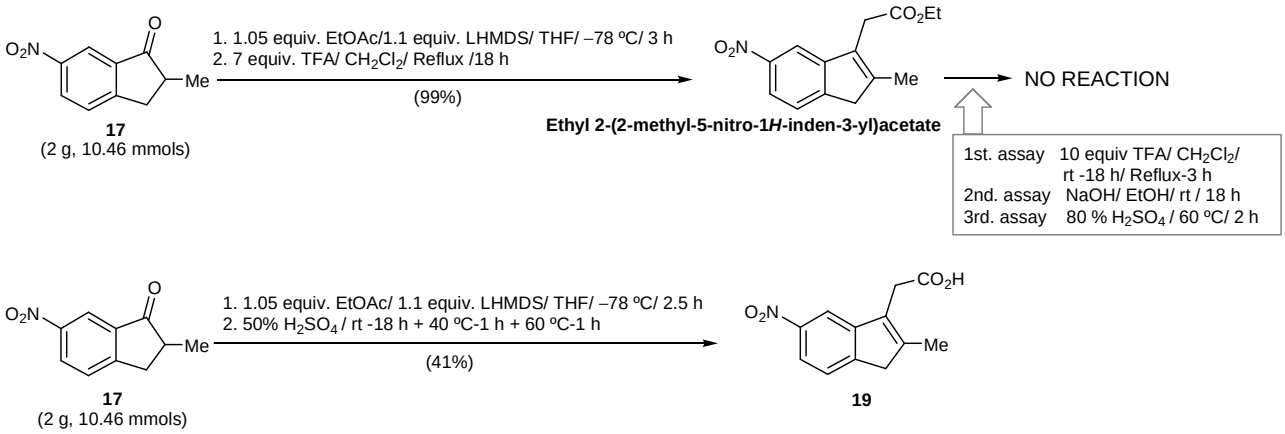
## SYNTHESIS OF INDEN-5-AMINES 23–28

- **(2-Methyl-5-nitro-1*H*-inden-3-yl)acetic acid 19. Others assays**




**17**
(2 g, 10.46 mmols)

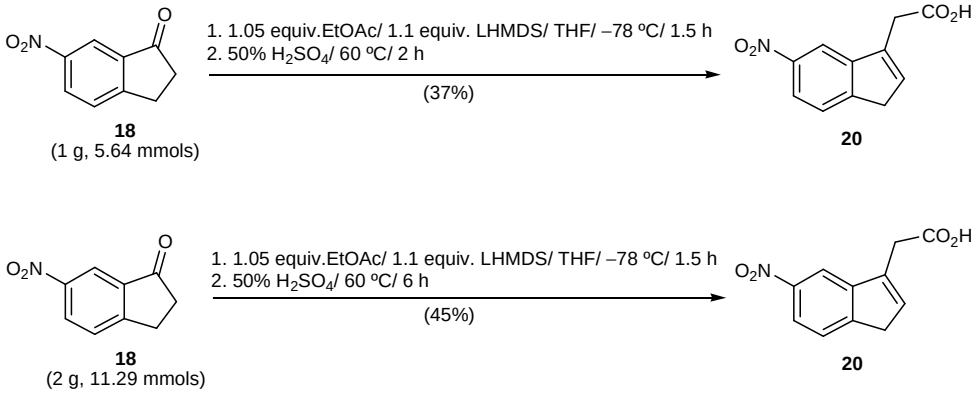
**Ethyl 2-(2-methyl-5-nitro-1*H*-inden-3-yl)acetate**

**19**

### Ethyl (2-methyl-5-nitro-1*H*-inden-3-yl)acetate

$^1$H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, $J$ = 7.4 Hz, 3H), 2.17 (s, 3H), 3.44 (s, 2H), 3.57 (s, 2H), 4.17 (q, $J$ = 7.4 Hz, 2H), 7.39-7.47 (m, 1H), 7.96-8.09 (m, 2H) ppm. $^{13}$C NMR ($CDCl_3$, 50.3 MHz): δ 14.2 ($CH_3$), 14.3 ($CH_3$), 31.3 ($CH_2$), 42.8 ($CH_2$), 61.2 ($CH_2$), 113.3 (CH), 119.5 (CH), 123.2 (CH), 125.4, 129.4, 145.5, 147.2, 149.0, 170.3 (C=O) ppm.

- **(5-Nitro-1*H*-inden-3-yl)acetic acid 20. Others assays**



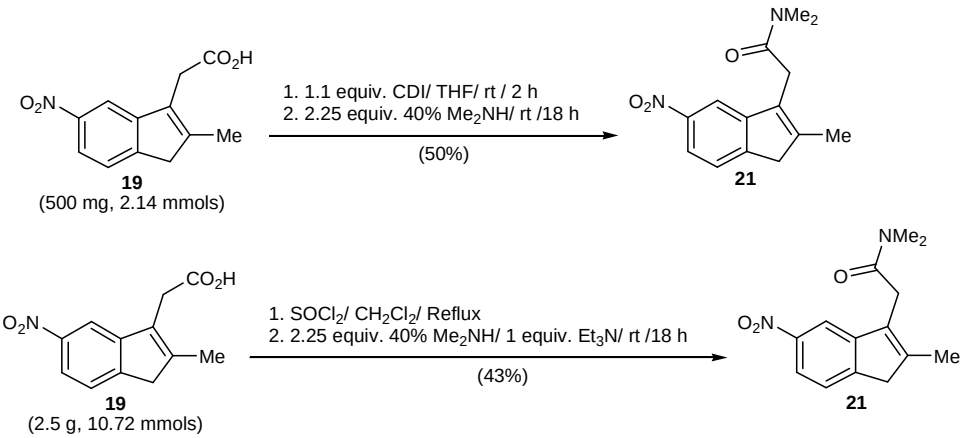

**18**
(1 g, 5.64 mmols)

**20**

**18**
(2 g, 11.29 mmols)

**20**

- ***N,N*-Dimethyl-2-(2-methyl-5-nitro-1*H*-inden-3-yl)acetamide 21. Others assays**



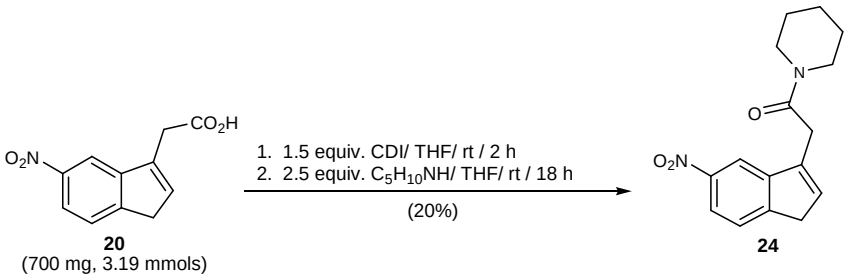

**19**
(500 mg, 2.14 mmols)

**21**

**19**
(2.5 g, 10.72 mmols)

**21**

- **1-[(5-Nitro-1*H*-inden-3-yl)acetyl]piperidine 24. Others assays**

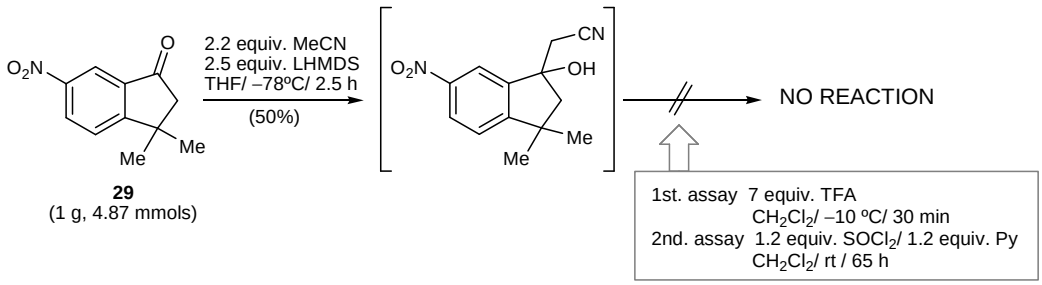



**20**
(700 mg, 3.19 mmols)

**24**

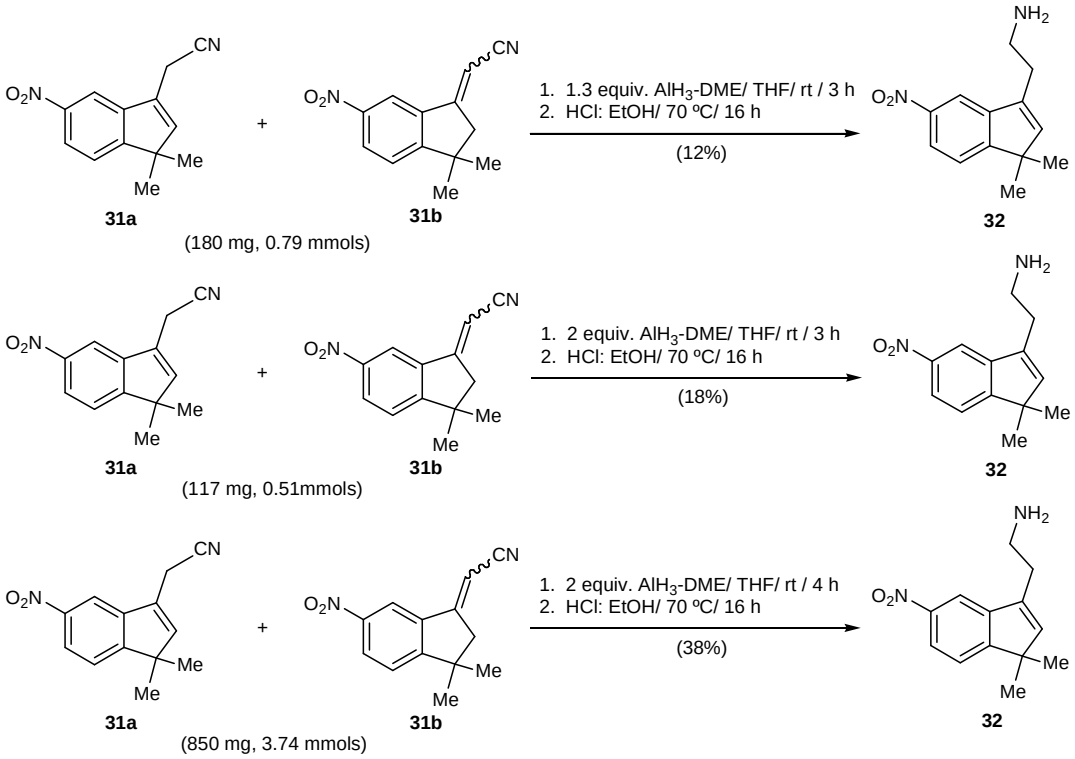
## SYNTHESIS OF INDEN-5-AMINE 34

- **(1,1-Dimethyl-5-nitro-1*H*-inden-3-yl)acetonitrile 31a and (3,3-dimethyl-6-nitro-2,3-dihydro-1*H*-inden-1-ylidene)acetonitrile 31b**



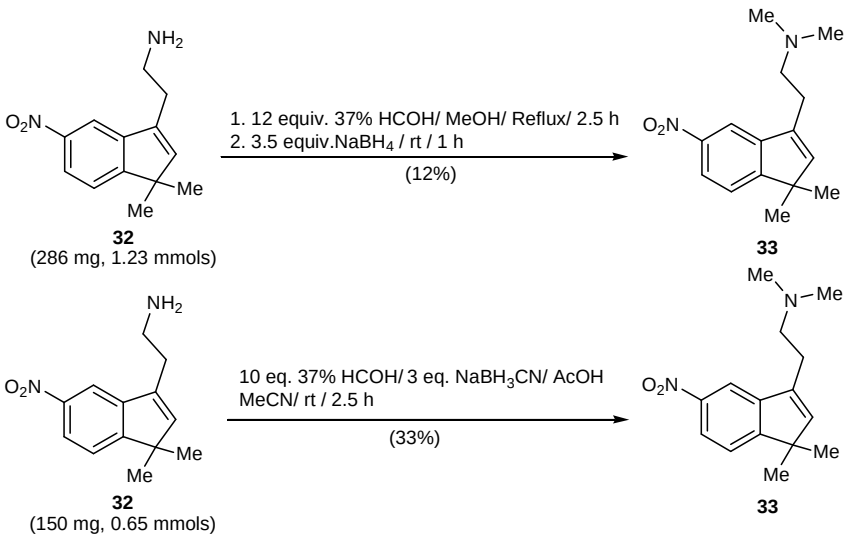

**29**
(1 g, 4.87 mmols)

- **2-(1,1-Dimethyl-5-nitro-1*H*-inden-3-yl)ethanamine 32. Others assays**




**31a** **31b** **32**
(180 mg, 0.79 mmols)
(117 mg, 0.51mmols)
(850 mg, 3.74 mmols)

- **2-(1,1-Dimethyl-5-nitro-1*H*-inden-3-yl)-*N*,*N*-dimethylethanamine 33. Others assays**

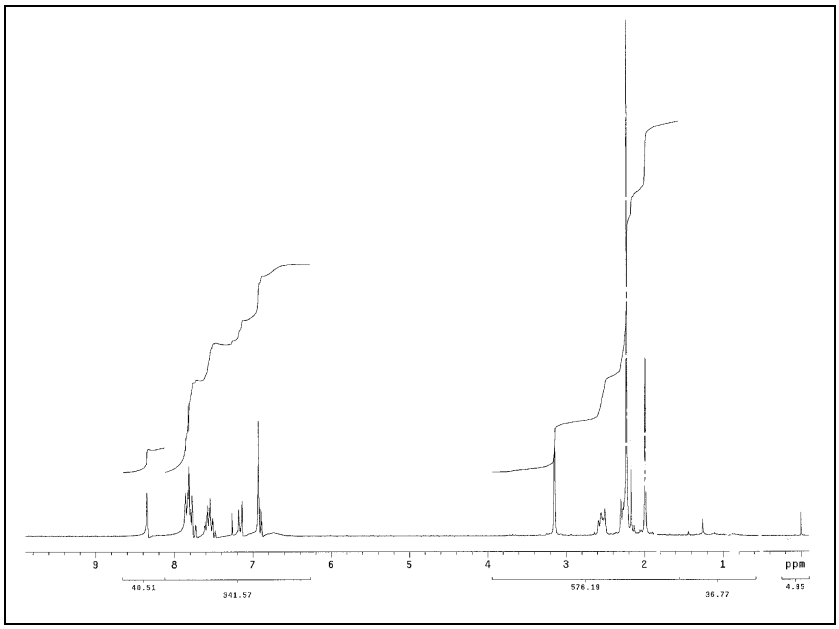



**32**
(286 mg, 1.23 mmols)
(150 mg, 0.65 mmols)
**33**

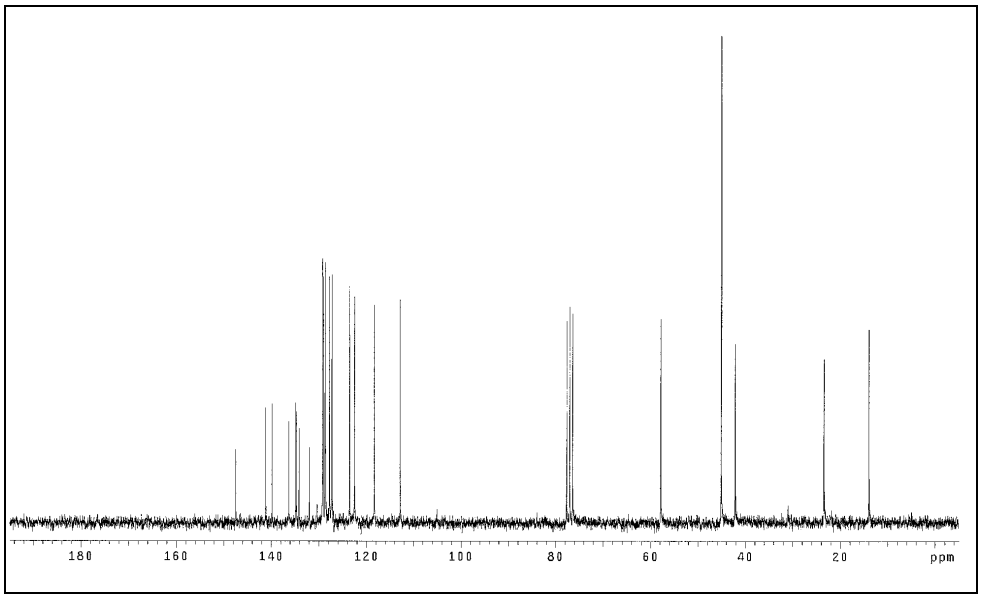
**NMR SPECTRA AND ESI(+)-HRMS SPECTRA OF TARGETED COMPOUNDS**

- ***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-2-sulfonamide 14**

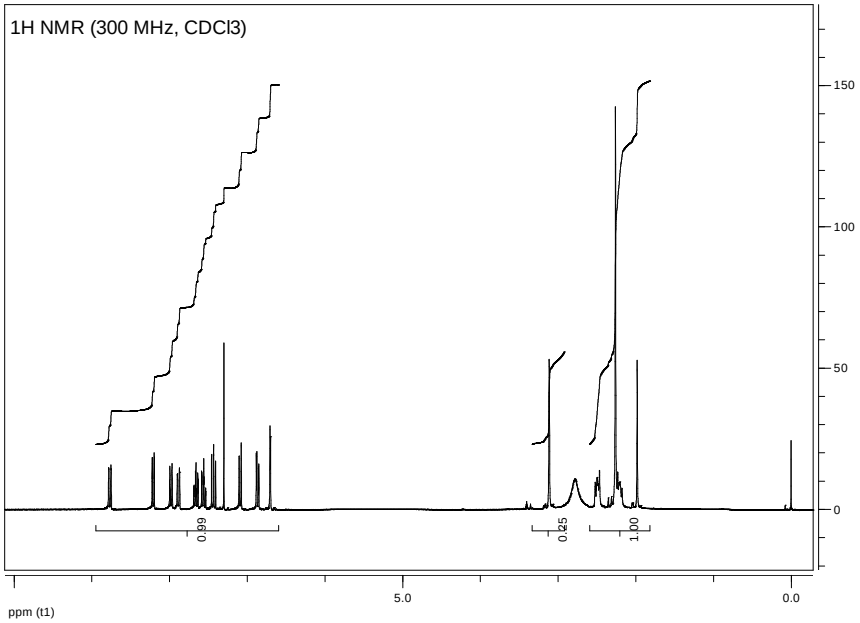
$^{1}$H NMR (200 MHz, $CDCl_3$)

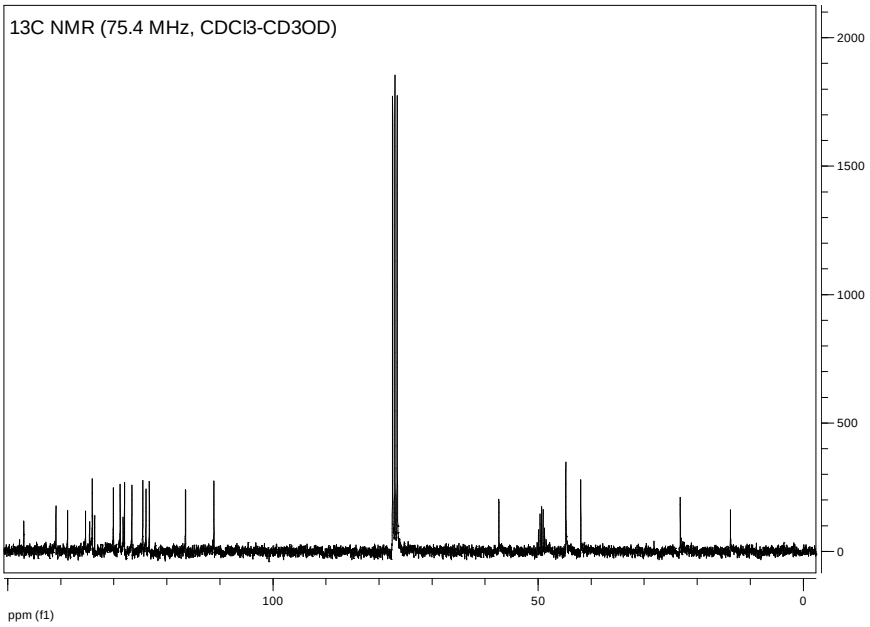


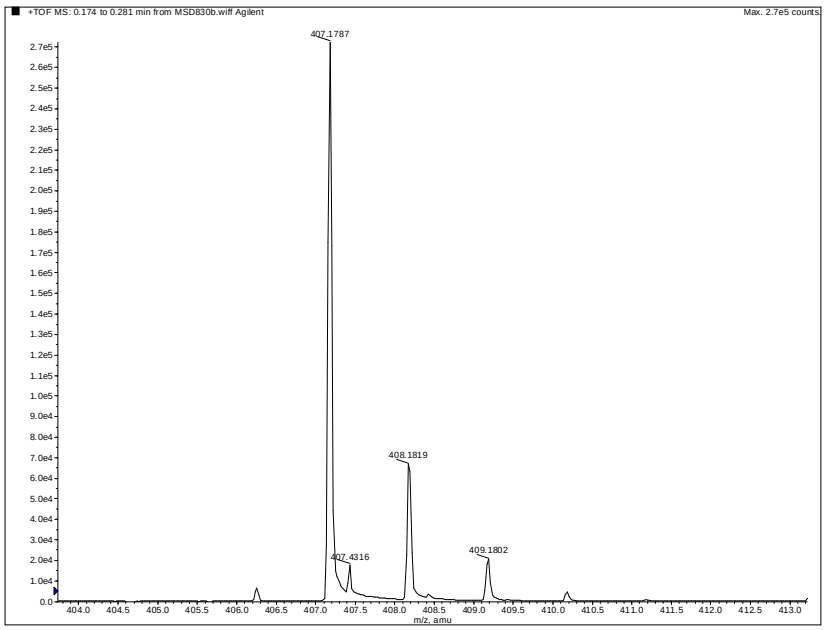

$^{13}$C NMR (50.3 MHz, $CDCl_3$)



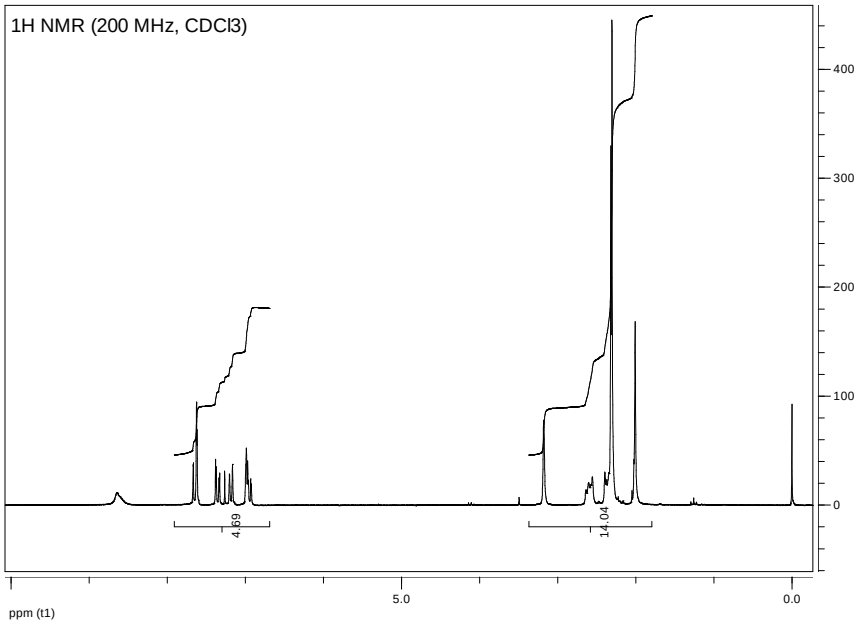
- ***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}naphthalene-1-sulfonamide 35**

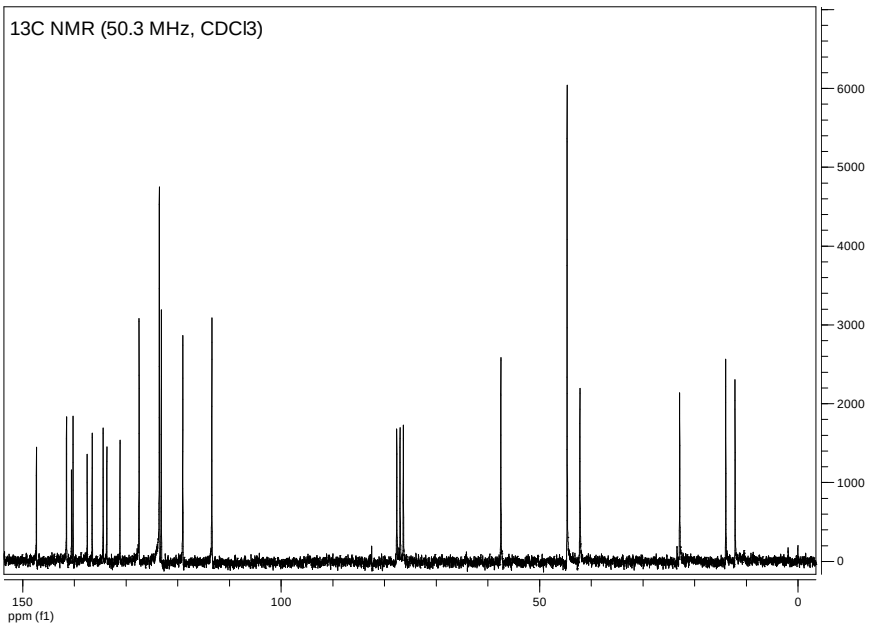


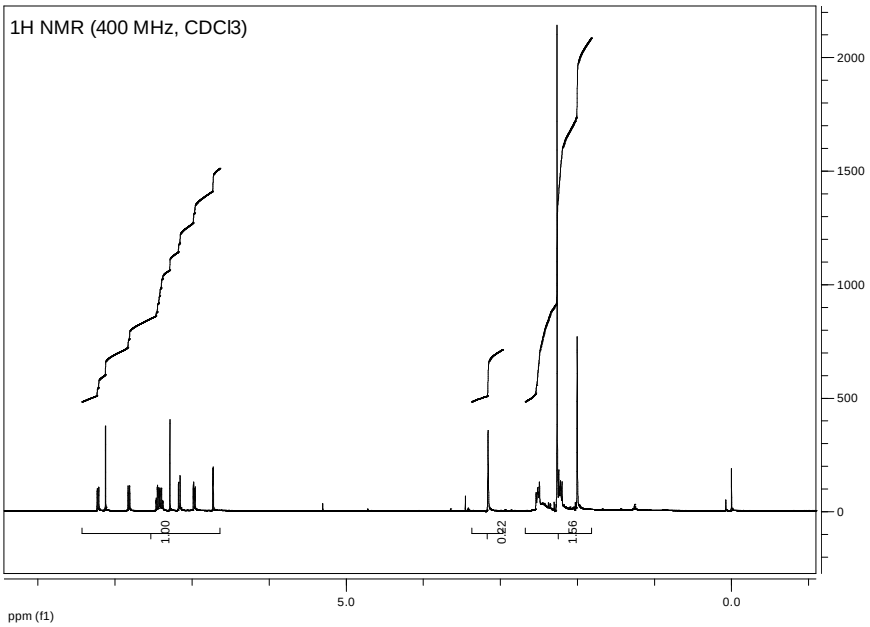



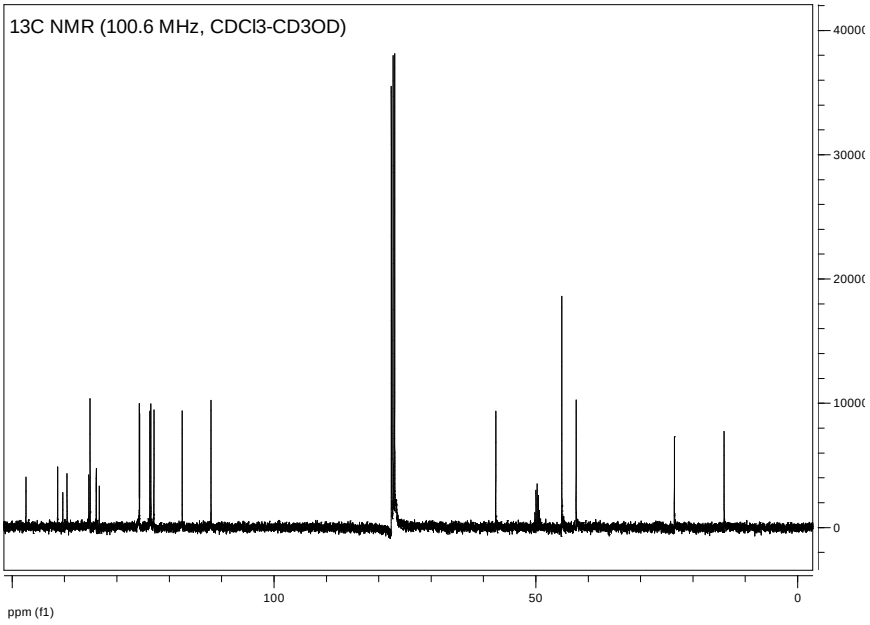
- **5-Chloro-*N*-{3-[2-(dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}-3-methyl-1-benzothiophene-2-sulfonamide 36**

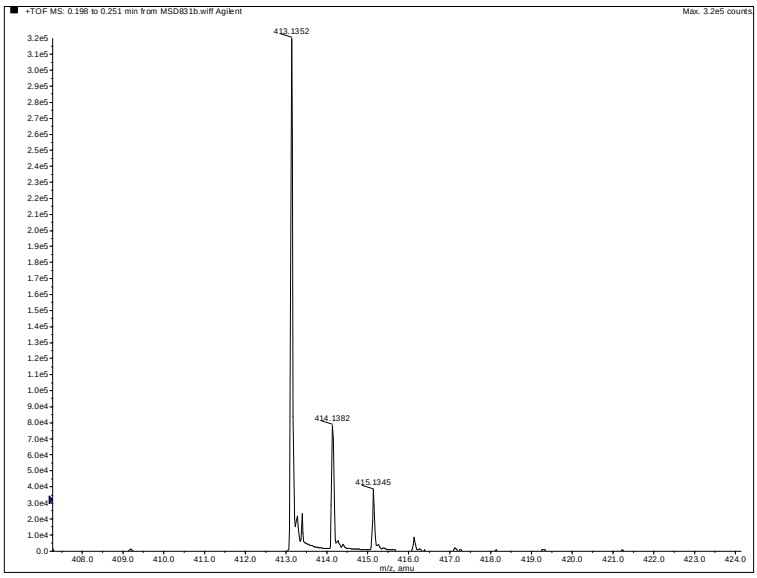


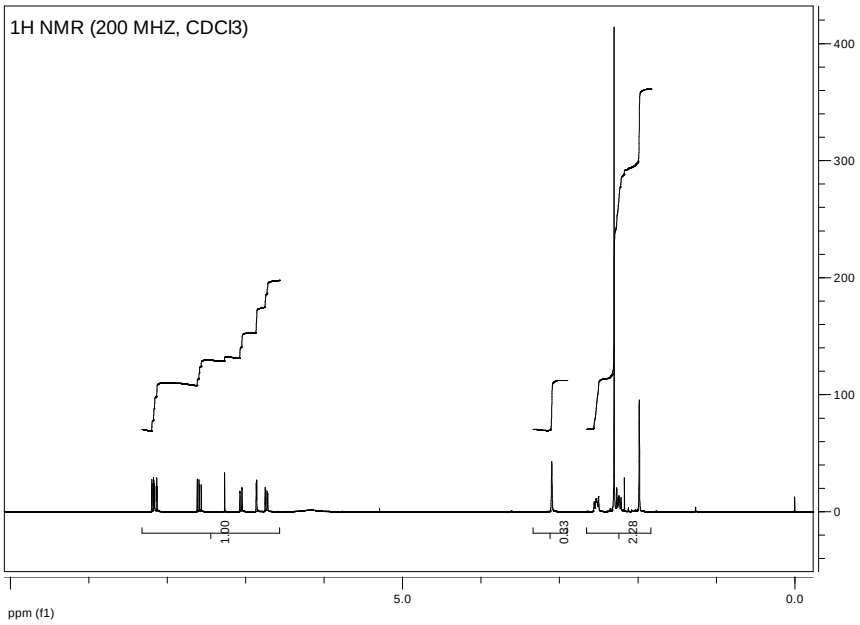
- ***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}-1-benzothiophene-3-sulfonamide 37**

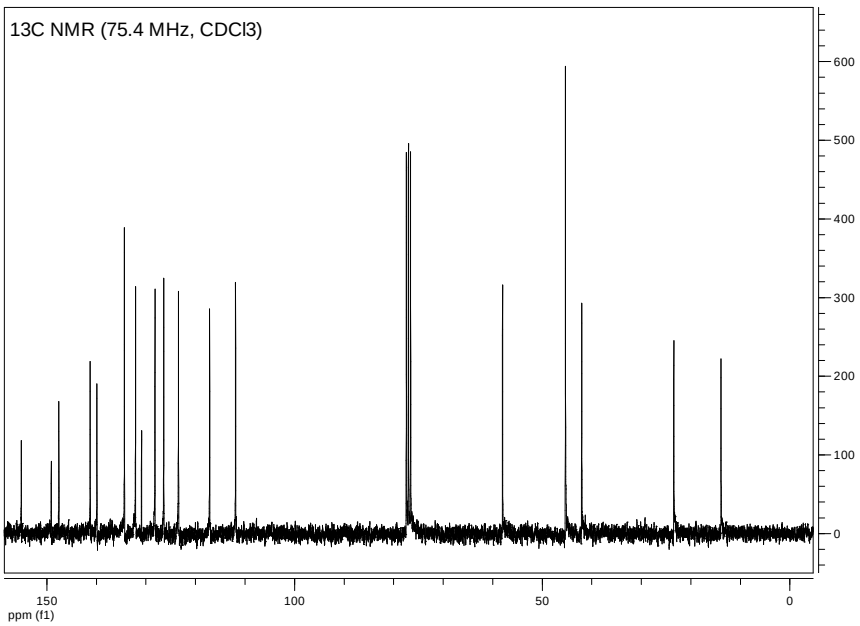


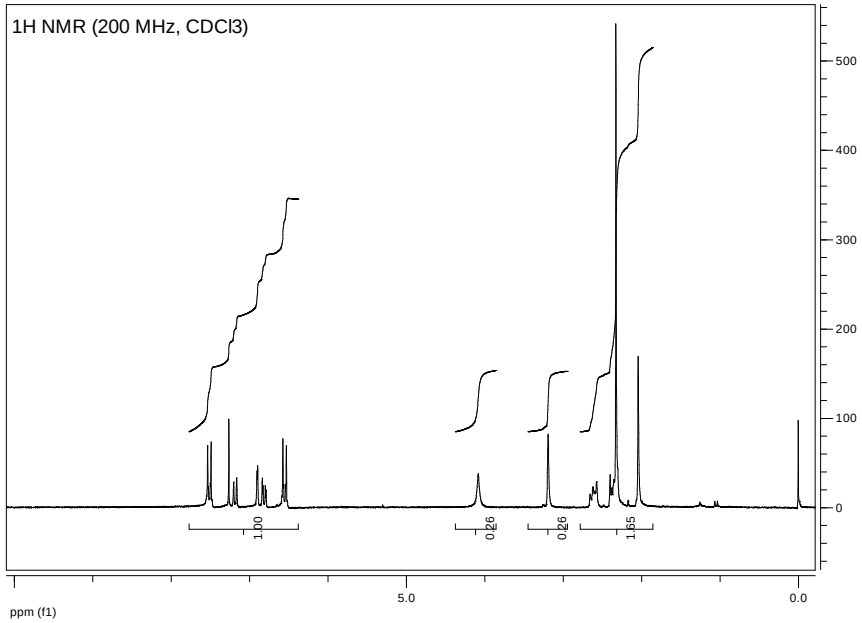



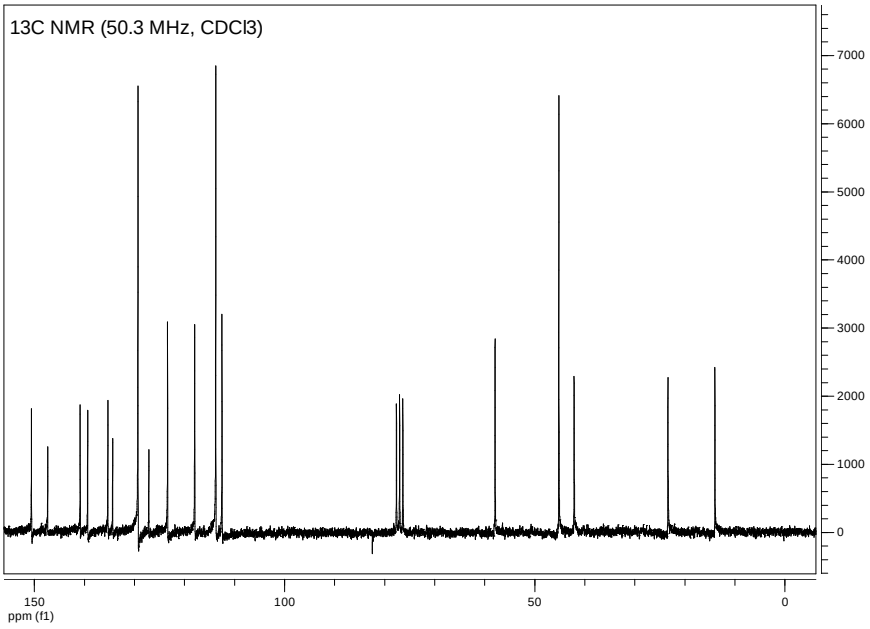
- ***N*-{3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}benzo[1,2,5]thiadiazole-4-sulfonamide 38**



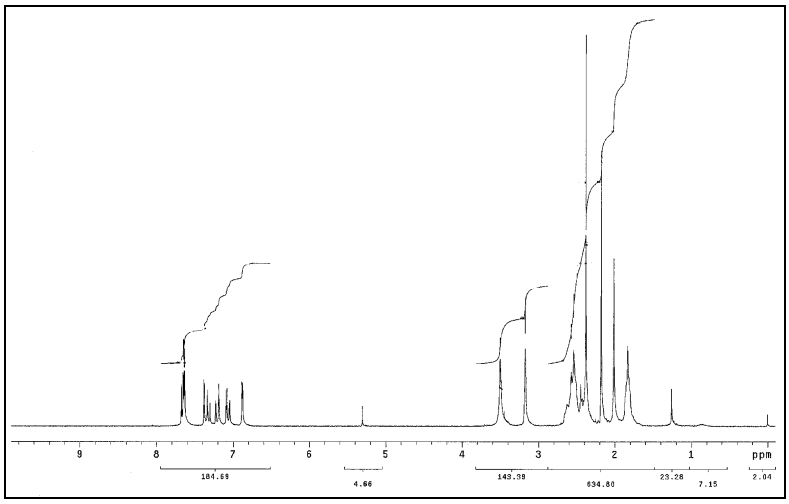
- **4-Amino-*N*-{3-[2-(dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}benzenesulfonamide 39**



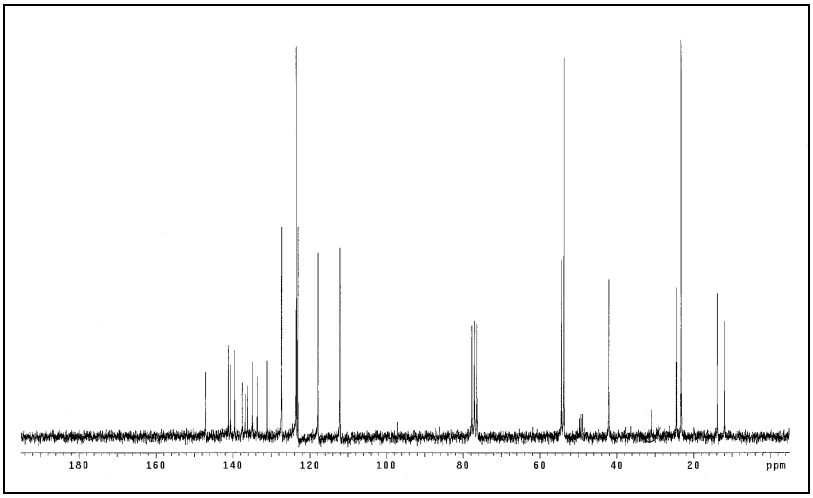



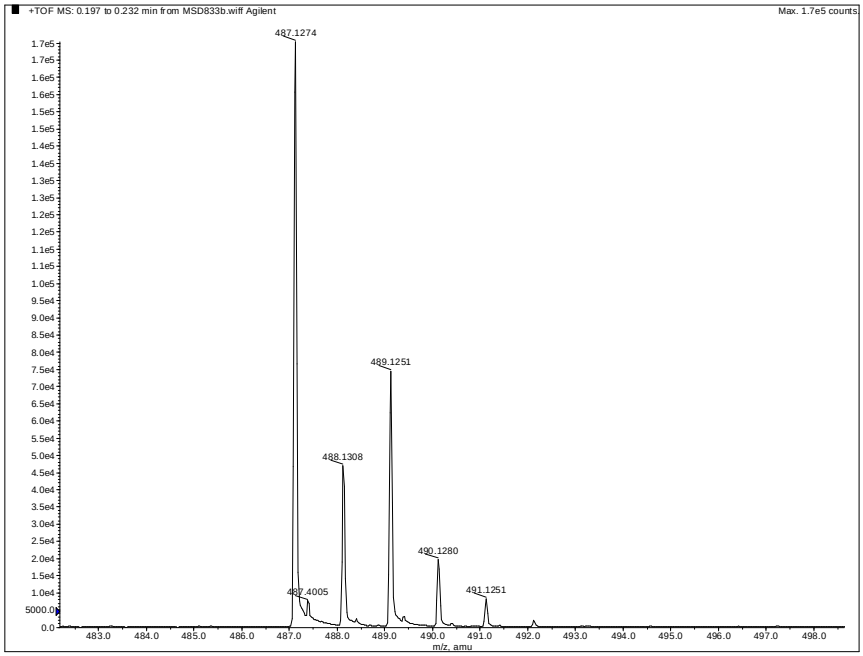
- **5-Chloro-3-methyl-*N*-[2-methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]-1-benzothiophene-2-sulfonamide 15**

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

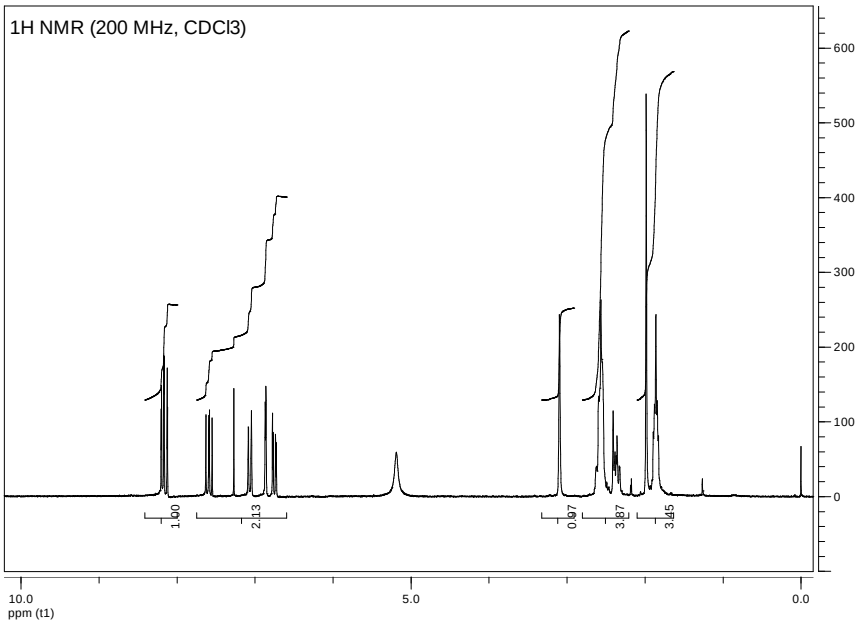


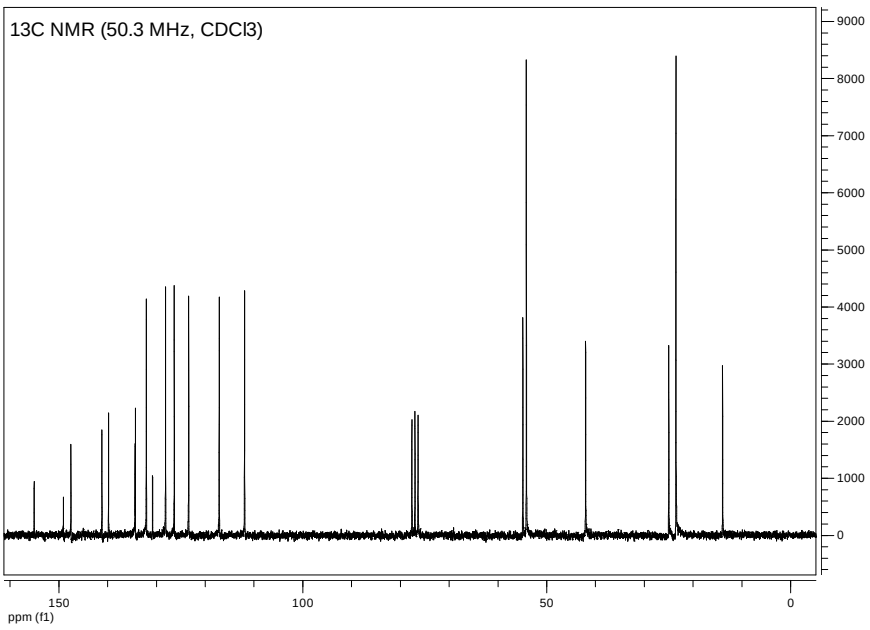

$^{13}$C NMR (50.3 MHz, $CDCl_3$)



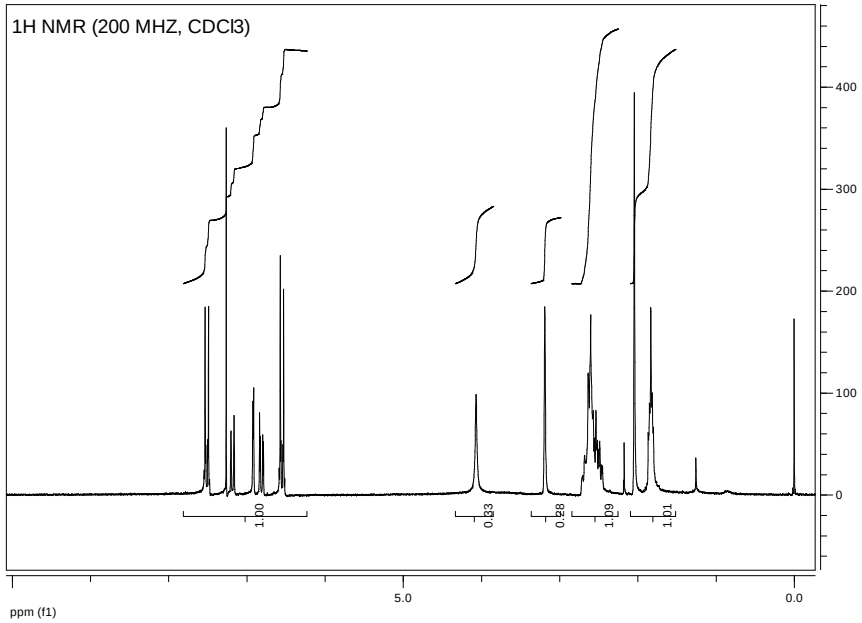



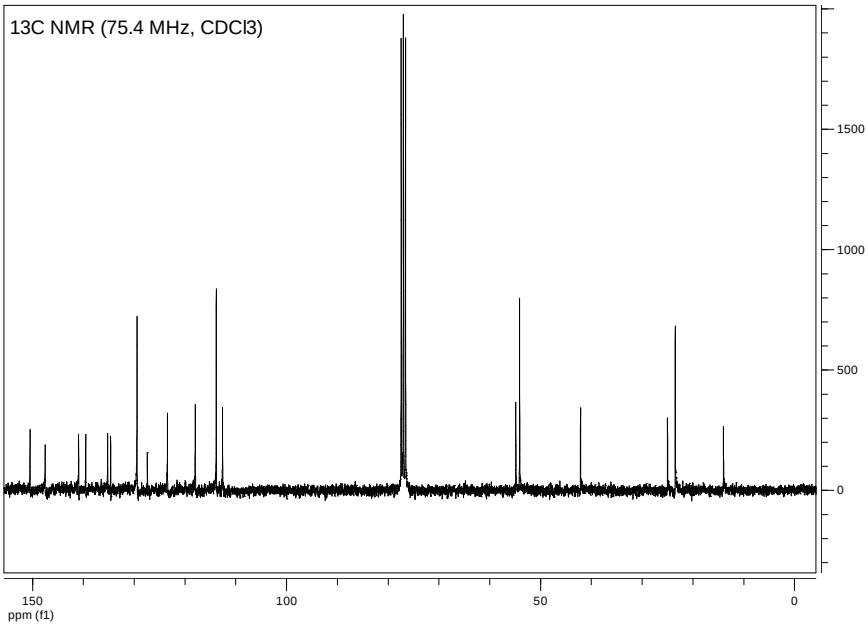
- ***N*-[2-Methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]benzo[1,2,5]thiadiazole-4-sulfonamide 40**



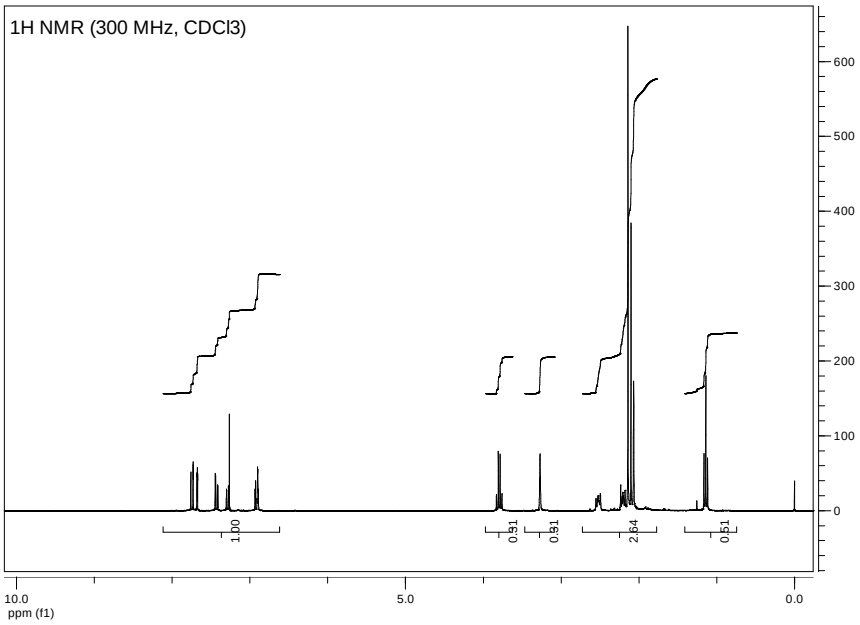



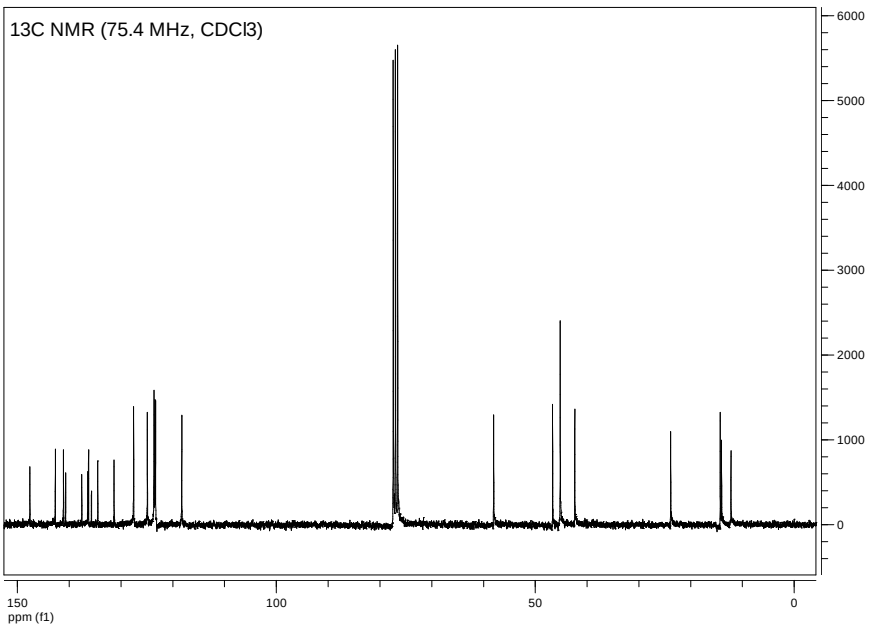
- **4-Amino-*N*-[2-methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]benzenesulfonamide 41**



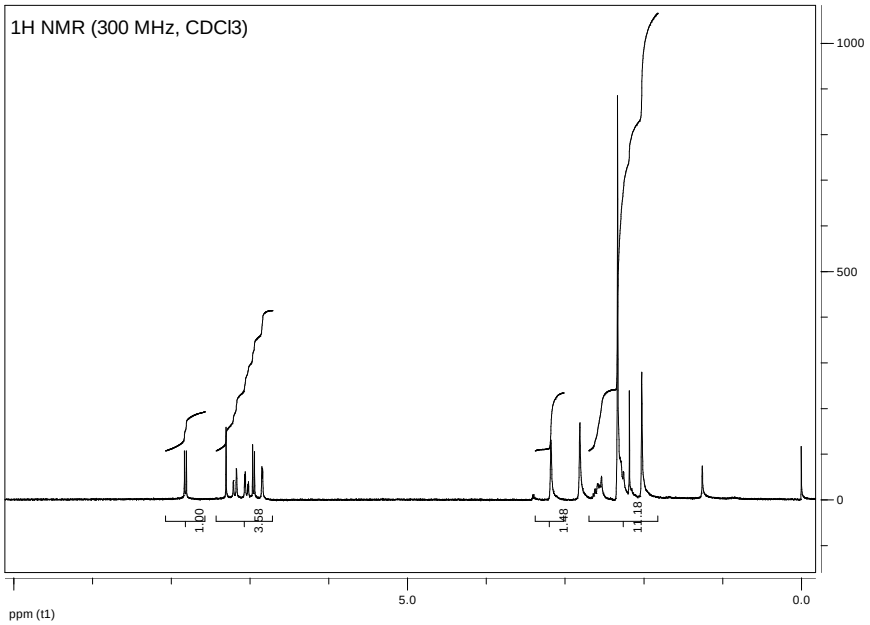



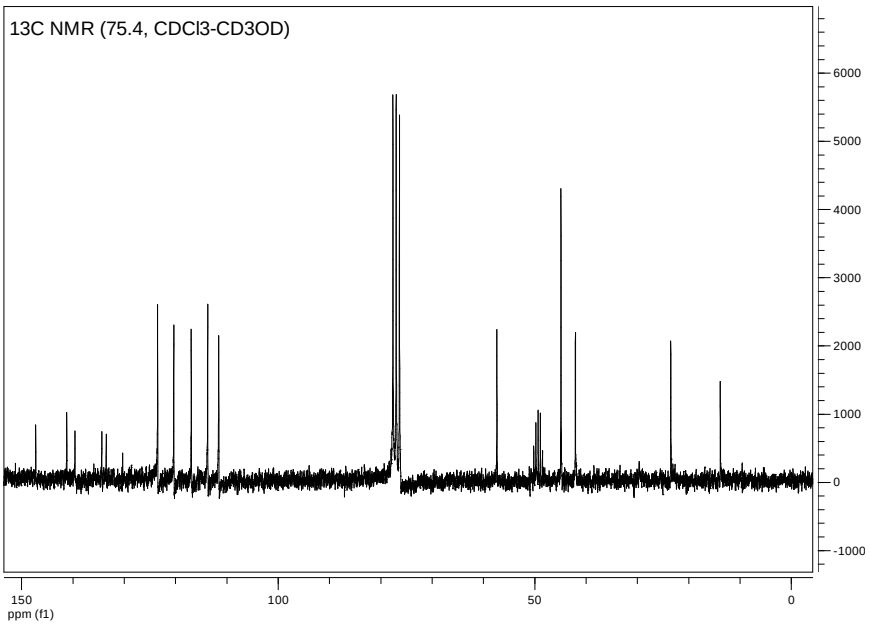
- **5-Chloro-*N*-[3-(2-dimethylaminoethyl)-2-methyl-1*H*-inden-5-yl]-*N*-ethyl-3-methylbenzo[*b*]thiophene-2-sulfonamide 42**

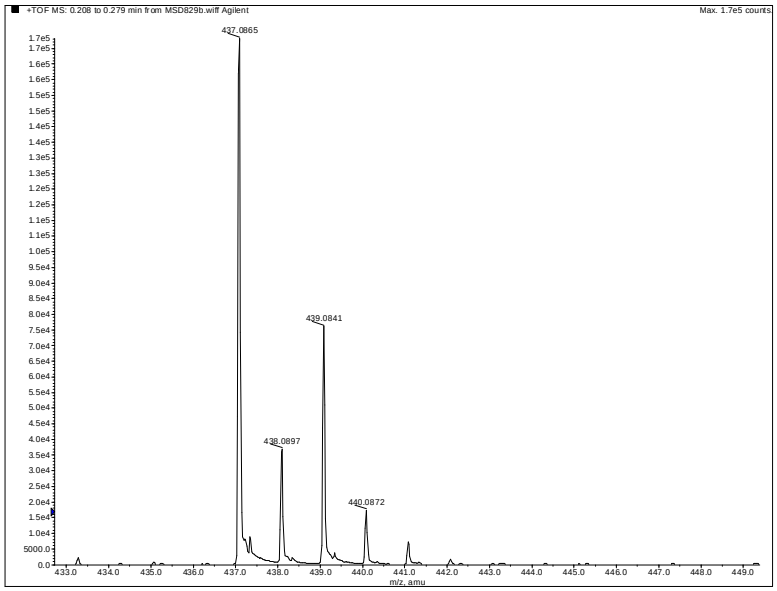


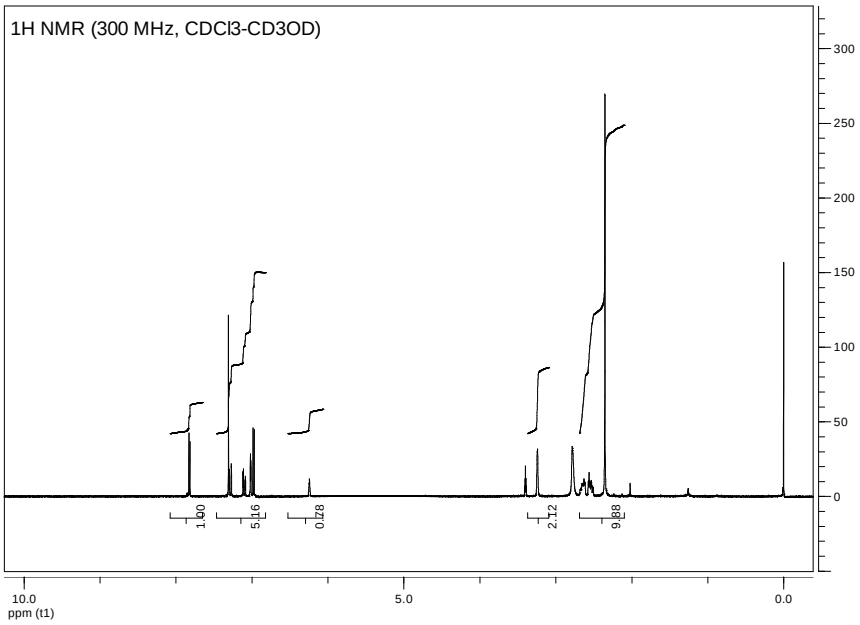
- **6-Chloro-*N*-{3-[2-(dimethylamino)ethyl]-2-methyl-1*H*-inden-5-yl}imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 43**

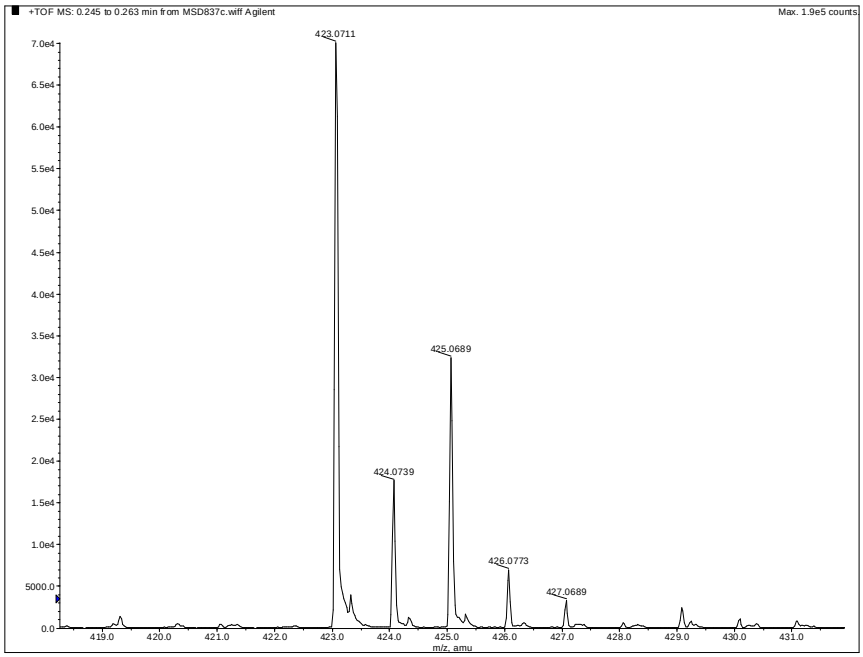


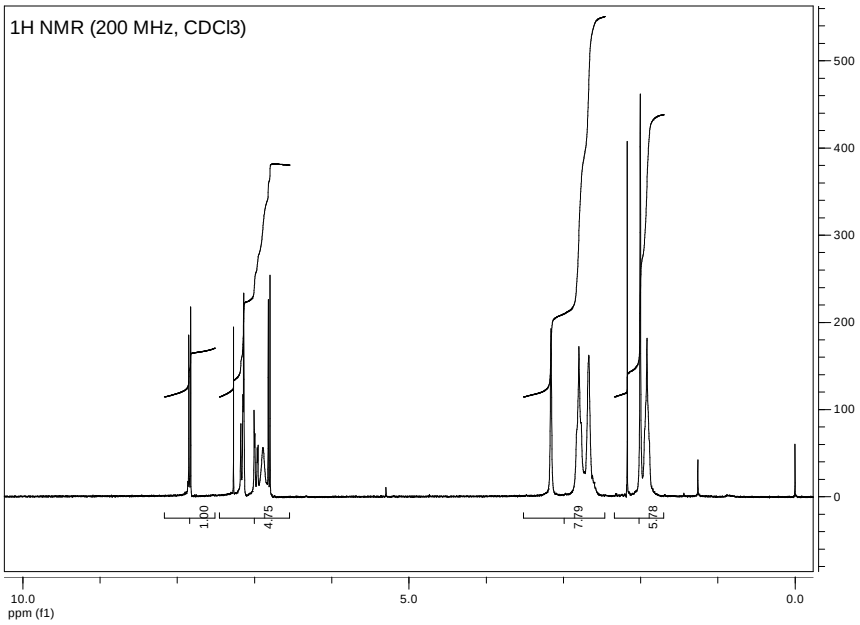



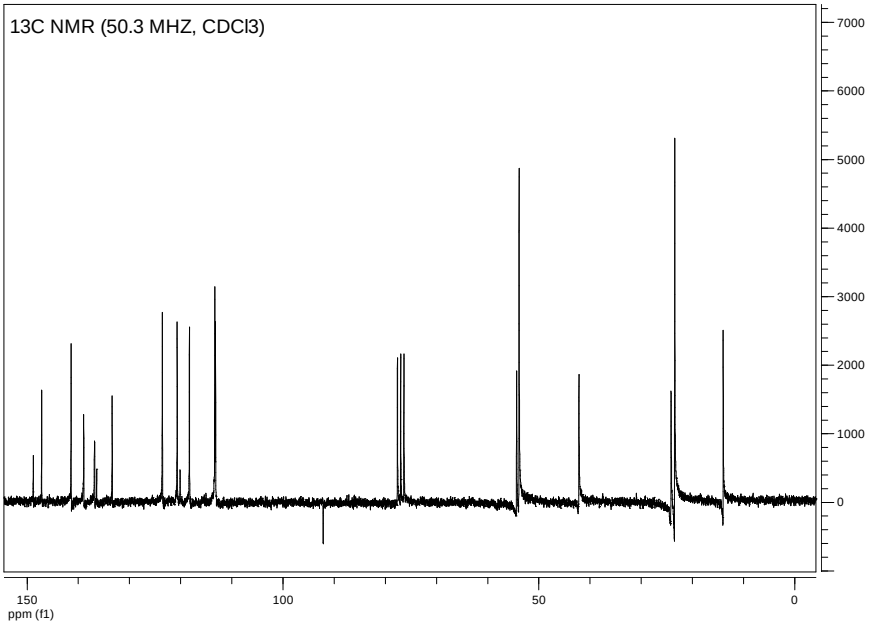
- **6-Chloro-*N*-{3-[2-(dimethylamino)ethyl]-1*H*-inden-5-yl}imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 44**



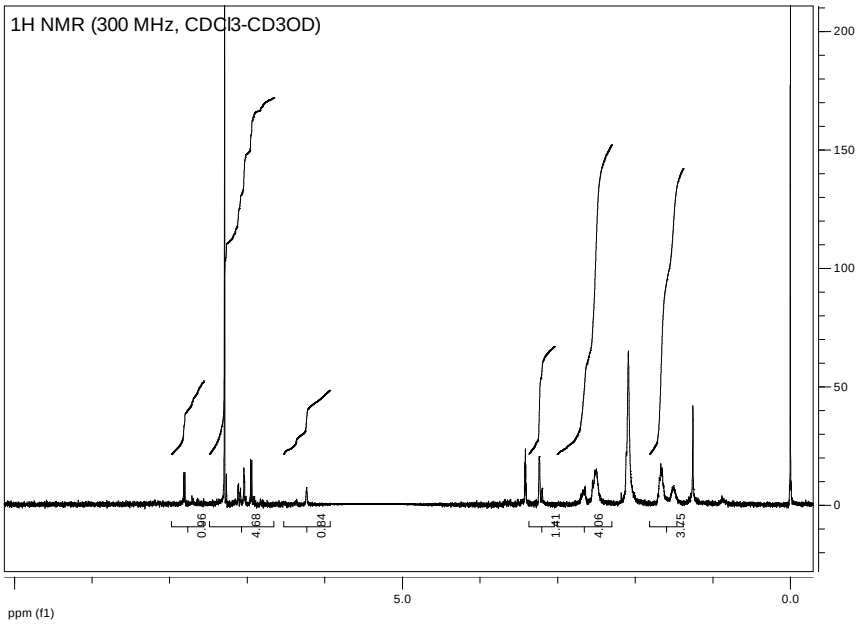



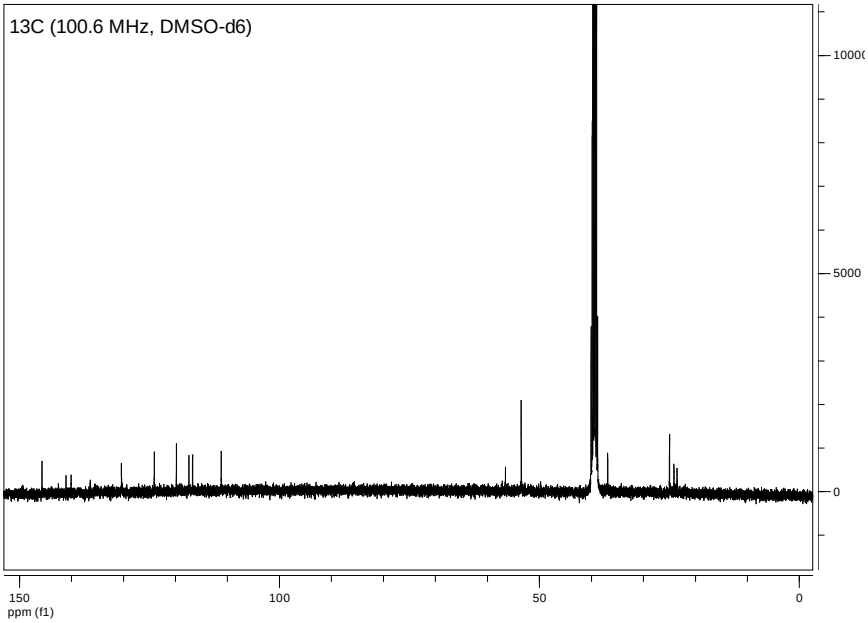
- **6-Chloro-*N*-[2-methyl-3-(2-pyrrolidin-1-ylethyl)-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 45**

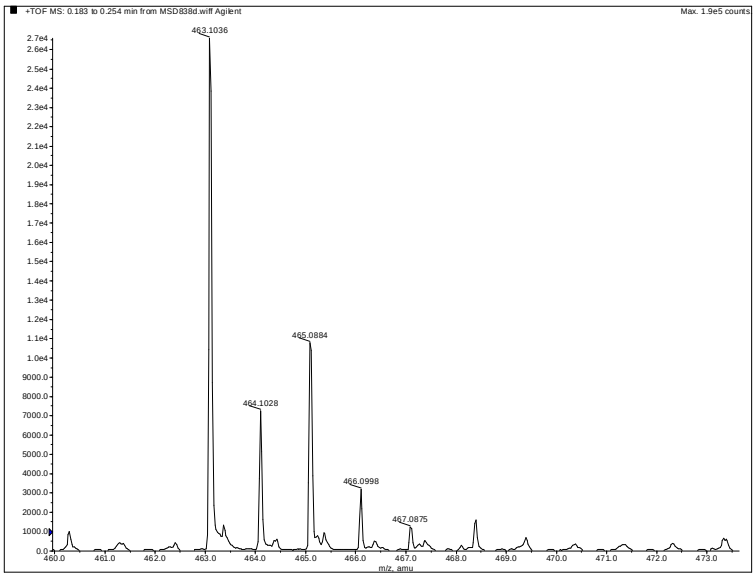


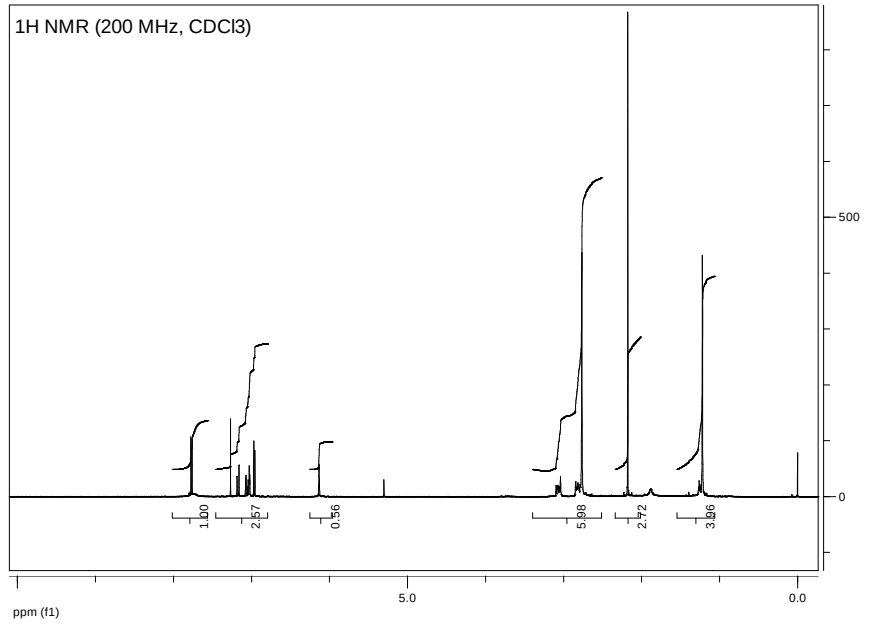
- **6-Chloro-*N*-[3-(2-piperidin-1-ylethyl)-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 46**

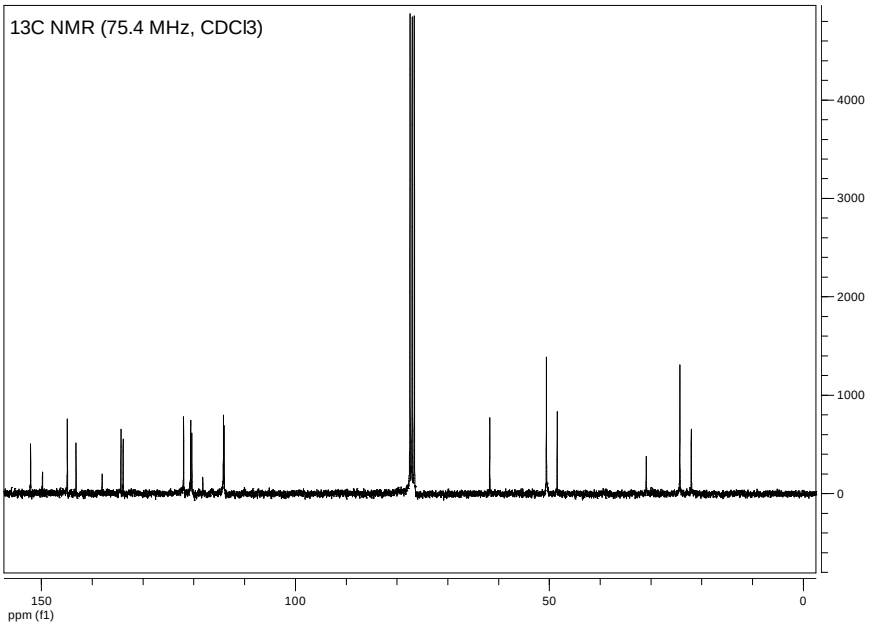


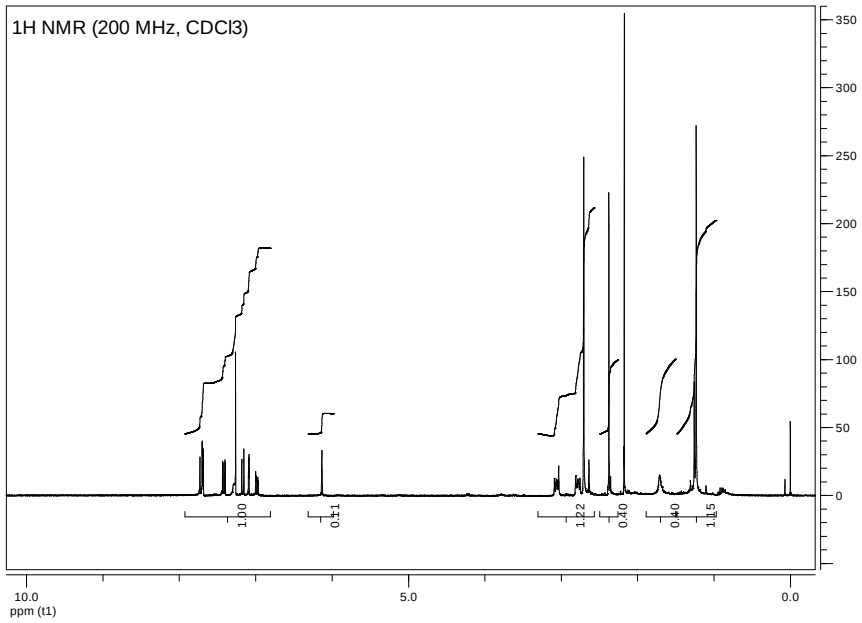



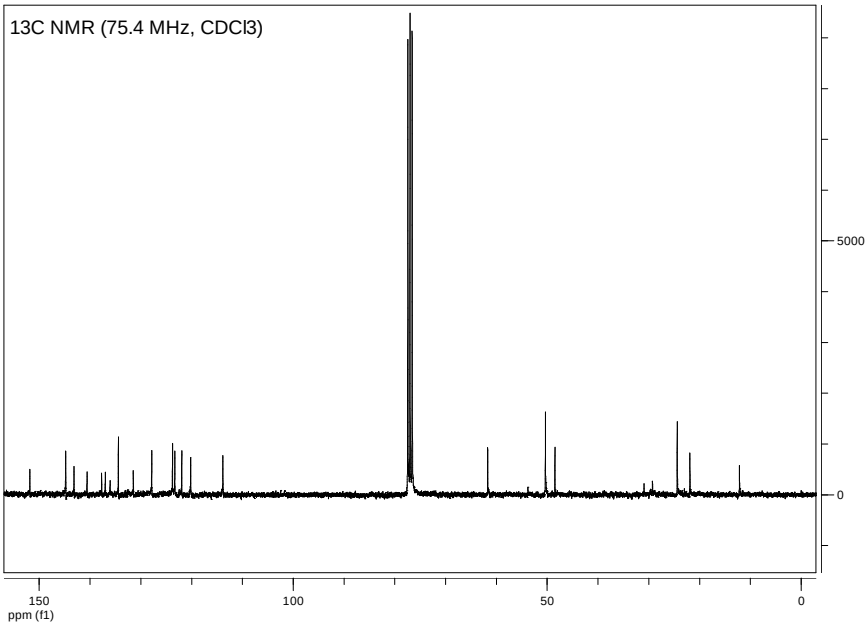
- **6-Chloro-*N*-{3-[2-(dimethylamino)ethyl]-1,1-dimethyl-1*H*-inden-5-yl}imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 47**



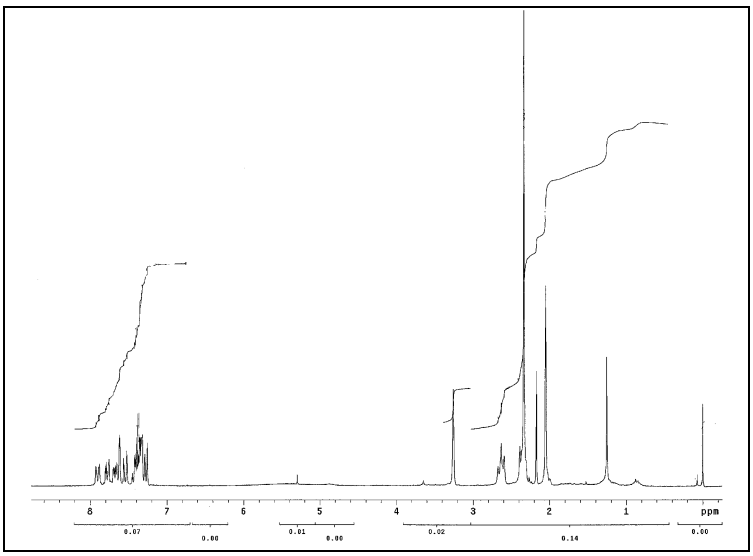
- **5-Chloro-*N*-{3-[2-(dimethylamino)ethyl]-1,1-dimethyl-1*H*-inden-5-yl}-3-methylbenzo[*b*]thiophene-2-sulfonamide 48**



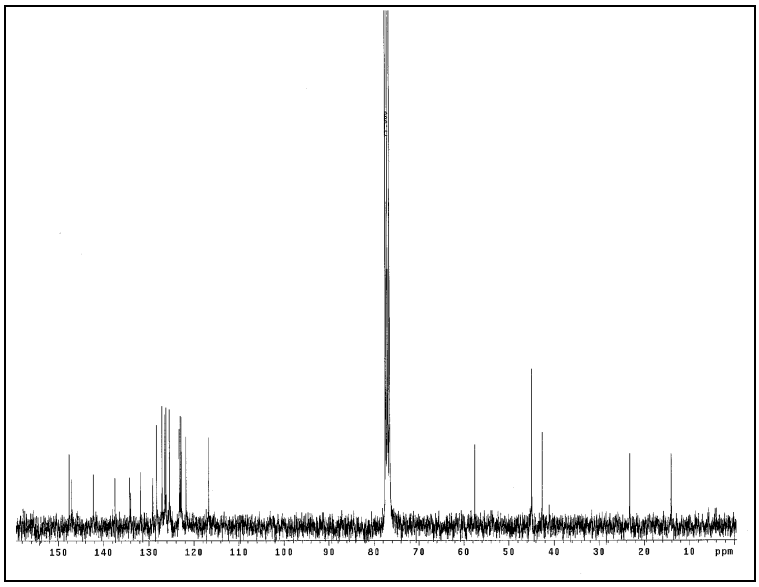



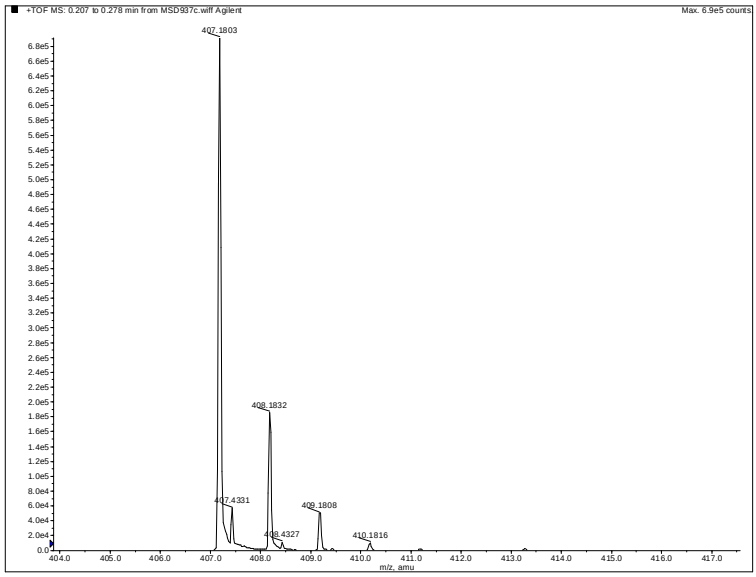
- **3-[2-(Dimethylamino)ethyl]-2-methyl-*N*-naphth-1-yl-1*H*-indene-5-sulfonamide 54**

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




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



**ELEMENTAL ANALYSIS OF TARGETED COMPOUNDS**

| Cpd. | Calculated | | | | Found | | | |
|---|---|---|---|---|---|---|---|---|
| | % C | % H | % N | % S | % C | % H | % N | % S |
| **14** | 60.30 | 5.68 | 5.60 | 6.41 | 60.12 | 5.32 | 5.26 | 6.21 |
| **36** | 58.21 | 5.63 | 5.90 | 13.51 | 58.35 | 5.32 | 6.06 | 13.43 |
| **38** | 57.13 | 5.43 | 13.32 | 15.25 | 57.10 | 5.28 | 13.28 | 15.10 |
| **39** | 62.50 | 7.24 | 10.41 | 7.94 | 62.18 | 6.86 | 10.34 | 7.56 |
| **40** | 56.51 | 5.82 | 11.98 | 13.71 | 56.31 | 5.86 | 12.13 | 13.72 |
| **41** | 64.31 | 7.27 | 9.78 | 7.46 | 63.91 | 7.51 | 10.17 | 7.09 |
| **42** | 59.21 | 6.16 | 5.52 | 12.64 | 58.98 | 5.87 | 5.76 | 12.41 |
| **45** | 49.47 | 5.57 | 10.99 | 12.58 | 49.18 | 5.20 | 11.02 | 12.41 |
| **47** | 51.22 | 5.37 | 11.95 | 13.67 | 50.89 | 5.20 | 12.05 | 13.41 |
| **48** | 58.46 | 5.93 | 5.68 | 13.00 | 58.18 | 5.86 | 5.32 | 12.61 |

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# Indene-based frameworks targeting the 5-HT$_6$ serotonin receptor: Ring constraint in indenylsulfonamides using cyclic amines and structurally abbreviated counterparts ☆

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ABSTRACT

Further studies in quest of 5-HT$_6$ serotonin receptor ligands led to the design and synthesis of a few selected examples of *N*-(inden-5-yl)sulfonamides with a ring-constrained aminoethyl side chain at the indene 3-position, some of which exhibited a high binding affinity, such as the pyrrolidine analogue **28** ($K_i$ = 3 nM). Moreover, the structurally abbreviated *N*-(inden-5-yl)sulfonamides showed $K_i$ values $\geqslant$43 nM, which indicates that neither the *N*,*N*-aminoethyl nor the conformationally restricted aminoethyl side arm at the indene 3-position are required for binding. Selected compounds were then tested in a functional cAMP stimulation assay and found to act as 5-HT$_6$ antagonists, although with moderate potency at the micromolar level.



## 1. Introduction

The 5-HT$_6$ serotonin receptor has become an attractive and promising therapeutic target for the development of new drug-like selective CNS agents. Its study is also important to obtain a clearer picture of its role in cognition and learning, certain types of neuropsychological and neuropsychiatric diseases such as affective disorders, schizophrenia and Alzheimer's disease, and the treatment of obesity and related metabolic disorders. Among the variety of highly potent and selective 5-HT$_6$ ligands reported to date, the majority have been identified as receptor antagonists, since moderate selectivity has been a major hurdle in the search for 5-HT$_6$ agonists.[2–4] Despite the intensive research dedicated to finding small-molecule 5-HT$_6$ ligands, only a very limited number (nine antagonists) have progressed to clinical development.[3a] From early lead $N_1$-arylsulfonyltryptamine ligands targeting the 5-HT$_6$ receptor,[2] for example, antagonist **1** (MS-245)[5,6] and agonist **2** (EMTD),[5] a variety of indole-based compounds have been reported, examples of selective agonists being **3** (E-6837)[7–9] and **4** (WAY-181187)[10,11] (Fig. 1).

The influence of the *N*,*N*-dimethylaminoethyl side chain at the indole 3-position has been examined using conformationally rigid counterparts in $N_1$-arenesulfonylindoles.[12,13] Yet when the $N_1$-arylsulfonyl motif was moved to a 5-amino substituent, the (pyrrolidinylmethylene)indole array showed different behavior towards the 5-HT$_6$ receptor, depending on the stereochemistry. Thus, the (*R*)-enantiomers were found to be potent and selective 5-HT$_6$ agonists, for example, (*R*)-**5a** (WAY-466) and (*R*)-**5b**, while the (*S*)-enantiomers displayed moderate antagonist activity, for example, (*S*)-**5b**.[14,15] Other conformationally constrained $N_1$-arylsulfonylindoles have been reported, such as pyrrolidinylindole antagonist **6** and piperidinylindole agonist **7**.[13] Moreover, Glennon and co-workers have shown that the amine-to-ring distance can be shortened, as in the $N_1$-benzenesulfonylgramine analog **8**,[16] while maintaining the affinity in $N_1$-arenesulfonylindole antagonists **9**[16] and **10**[17] (Fig. 1). Hence, the terminal amine of **1**-type ligands can be structurally abbreviated to form **9**-type and **10**-type ligands, which indicates that the aminoethyl functionality of the tryptamines is not required for binding.[16,17] In parallel, there have been few attempts to exploit computational methods to provide insight into how 5-HT$_6$ ligands interact with the 5-HT$_6$ receptor, the most recent study dealing with $N_1$-arylsulfonyltryptamines and analogues, for example, compounds **1** and **2**.[18]

☆ Indene-Based Scaffols. 3; see Ref. 1 for Part 2.

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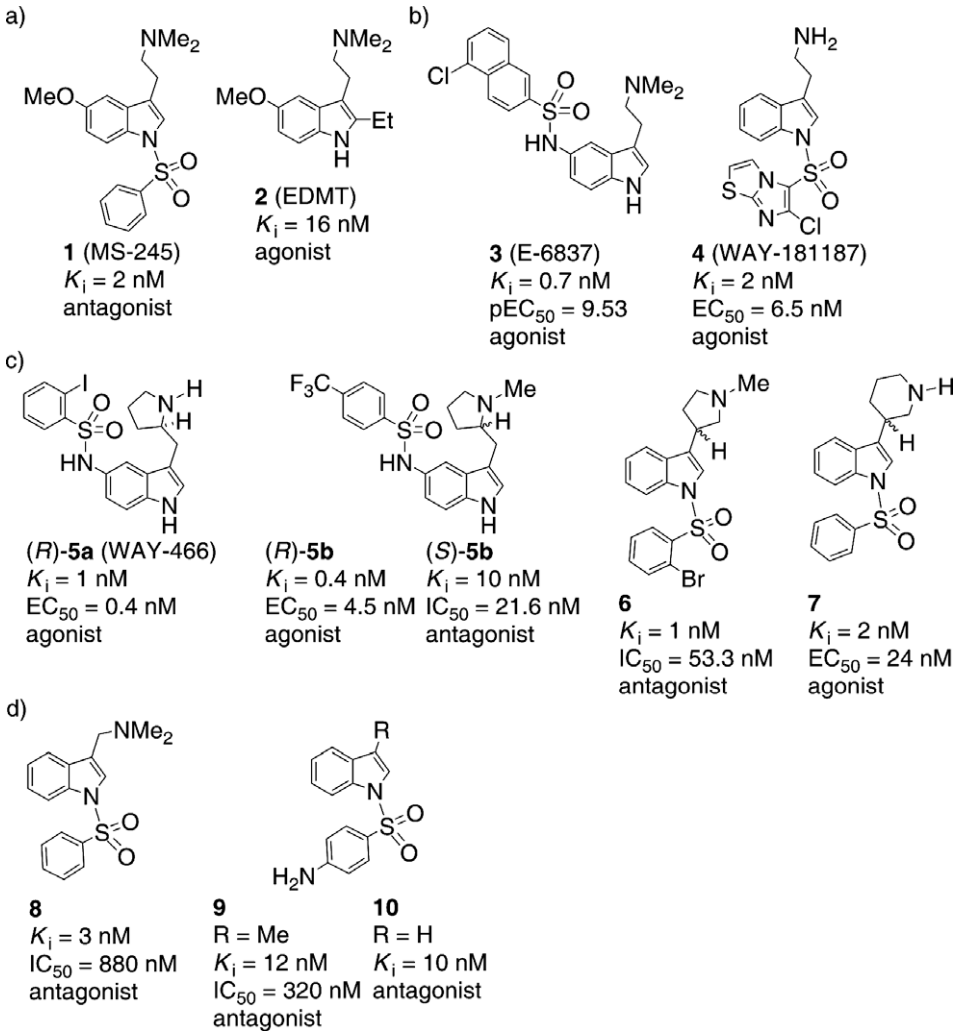



**Figure 1.** Indole-based 5-$HT_6$ serotonin receptor ligands: (a) early reference compounds, antagonist **1** (MS-245) and agonist **2** (EDMT); (b) examples of selective agonists **3** (E-6837) and **4** (WAY-181187); (c) conformationally constrained aminoethyl side chain in sulfonyltryptamines (*R*)-**5a** (WAY-466), (*R*)-**5b**, (*S*)-**5b**, **6** and **7**; (d) $N_1$-benzenesulfonylgramine analog **8** and $N_1$-arenesulfonylindole antagonists **9** and **10**.

We recently reported the design and synthesis of structural analogs based on an indole-to-indene switch from the potent and selective 5-$HT_6$ receptor indolylsulfonamides **11**[7,8] to indene counterparts, leading to the identification of a series of *N*-[3-(aminoethyl)inden-5-yl]sulfonamides **12**[1,19] with high binding affinity and acting as potent 5-$HT_6$ receptor agonists. This relationship can be illustrated by the following compound pairs: the 5-arylsulfonamide analog of tryptamine **13** (E-6801) and either the *N*-(inden-5-yl)sulfonamide **14** or **15** (Fig. 2). Seeking further insight into the application of indene-based ligands targeting the 5-$HT_6$ receptor,[20] we focused our attention on the ring-constrained **16**-type indenylsulfonamides as well as the structurally simplified **17**-type. A few indenylsulfonamides **16** and **17** were prepared and tested for affinity to the 5-$HT_6$ receptor, showing $K_i$ values $\geqslant$3 nM and $\geqslant$43 nM, respectively. Selected compounds inhibited 5-HT-stimulated cAMP production with micromolar antagonistic potencies.

## 2. Chemistry

The syntheses of the targeted indenylsulfonamides were carried out following the multi-step procedures shown in Schemes 1–3, starting from substituted indanones leading to the corresponding key indenamines, which permitted the preparation of compounds **16** to be diversified. Our first protocol to synthesize indenylsulfonamides **16** began with an aldol-type addition of the lithium salt of *N*-methyl-2-pyrrolidinone to nitroindanone **18**, whose immediate dehydration afforded (inden-3-yl)pyrrolidin-2-one **19** (see Supplementary data). Then, reduction of the amide group of **19** with $AlH_3$–$NMe_2Et$ complex and of the nitro group with zinc in acetic acid gave (pyrrolidin-3-yl)inden-5-amine **20**. Condensation of the lithium salt of *N*-methyl-2-piperidone with compound **18** gave (inden-3-yl)piperidin-2-one **21** and reduction of the amide and nitro groups of **21** afforded (piperidin-3-yl)inden-5-amine **22**. Following the same two-step sequence, nitroindanone **23** was transformed to (pyrrolidin-3-yl)inden-5-amine **25** (Scheme 1). Reaction of advanced inden-5-amines **20**, **22** and **25** with the appropriate sulfonyl chloride gave the constrained *N*-(inden-5-yl)sulfonamides **26**–**30** and reaction yields were not optimized.

The key inden-5-amines that would lead to the targeted structurally abbreviated **17**-type indenylsulfonamides were prepared by two synthetic routes using either aminoindan-1-ones or nitroindan-1-ones as starting materials (Scheme 2). Reduction of aminoindanone **31** with sodium borohydride and dehydration with sulfuric acid gave an isomeric mixture of indenamines **32** and **33** in good yield (90%). Using the same experimental procedure from aminoindanone **34**, a mixture of indenamines **35** and **36** was obtained in 80% yield. On the other hand, we have recently reported the conversion of nitroindanone **37** to the indenylacetic acid **38**

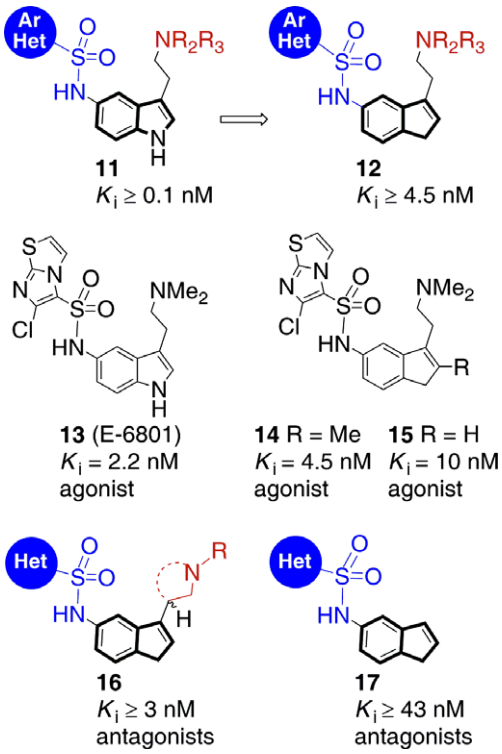



**Figure 2.** *N*-(Inden-5-yl)sulfonamides as novel 5-$HT_6$ serotonin receptor ligands: from *N*-[3-(aminoethyl)inden-5-yl]sulfonamides **12** to the conformationally rigid counterparts **16** and the structurally simplified *N*-(inden-5-yl)sulfonamides **17**.

involving an aldol-type reaction that proceeded in 27% yield.[1] Raising the dehydration temperature, compound **38** was obtained with lower yield together with the decarboxylated product **39**, whose nitro group was reduced with zinc in acetic acid to give inden-5-amine **40** (Scheme 2). α-Alkylation of 5-methoxyinda-1-one **41** afforded indanone **42**, which upon nitration gave a mixture of nitroindanones **43** and **44**. Aldol-type condensation of indanone **43** with the lithium salt of ethyl acetate provided the decarboxylated nitroindene **45**, which upon reduction afforded inden-5-amine **46**. Decarboxylations of (3-indenyl)acetic acids under these experimental conditions were not further investigated.

Sulfonylation of indenamine mixtures **32** + **33** and **35** + **36** with 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride gave the structurally abbreviated *N*-(indenyl)sulfonamide mixtures **47** + **48** and **49** + **50** in a 7:3 ratio calculated by $^1$H NMR (see later). Similarly, sulfonylation of inden-5-amines **40** and **46** afforded *N*-(inden-5-yl)sulfonamides **51** and **52**, respectively (Scheme 3).

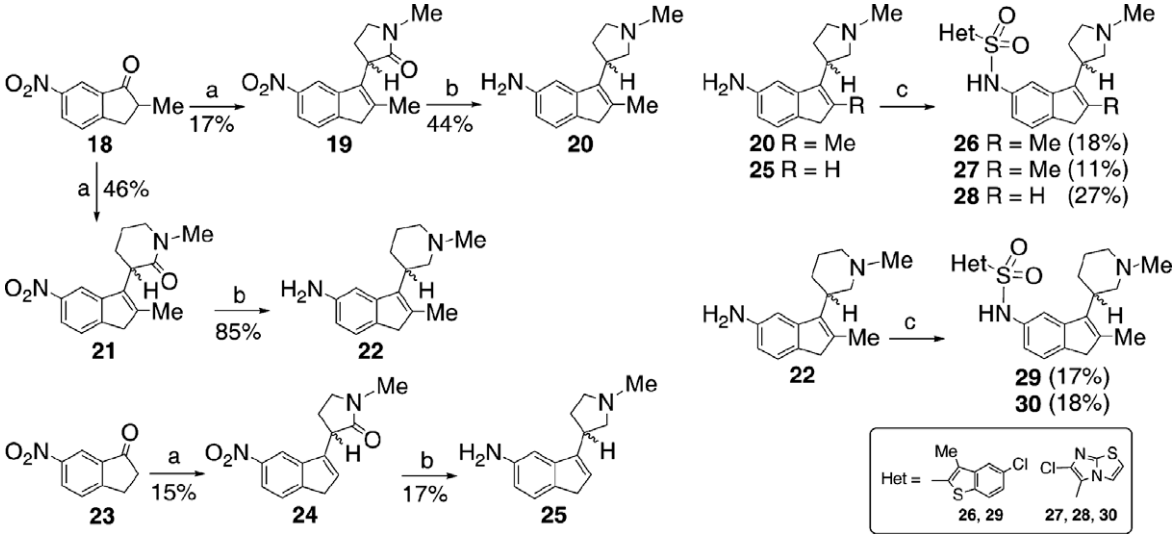
Depending on the difficulties encountered in the isolation and purification, chromatographic separations were generally required and sometimes a second chromatographic run was necessary. The quantity of new targeted compounds was variable but sufficient for the preliminary testing of their 5-$HT_6$ receptor affinity and functionality. Consequently, the reaction yields were not optimized.

The structure of the new indenylsulfonamides was confirmed by spectroscopic methods. Their $^1$H NMR and $^{13}$C NMR chemical shifts and physical data are gathered in Section 5.

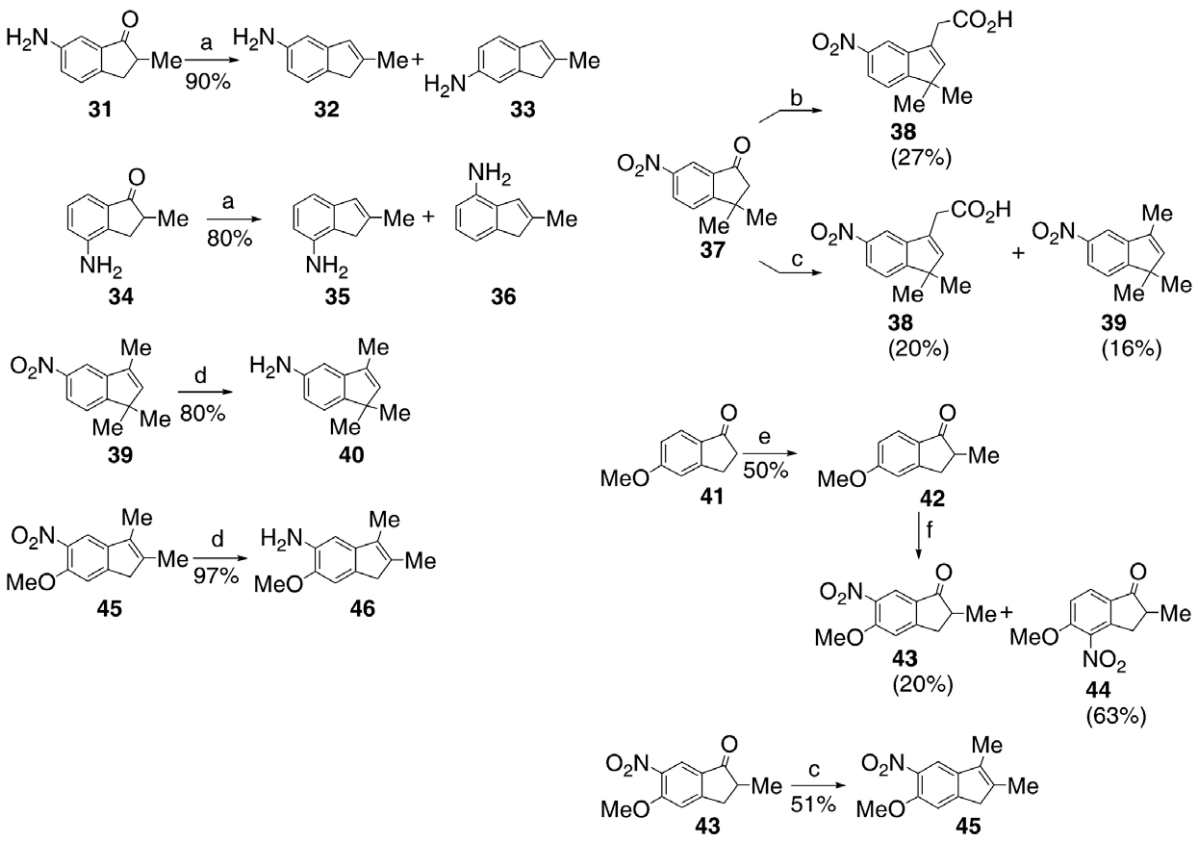
In the $^1$H NMR spectra recorded in $CDCl_3$ and DMSO-$d_6$ at 400 MHz, respectively, for the mixture of isomers **47** + **48**, the overlapping peaks could not be differentiated. However, the $^1$H NMR data in $CDCl_3$ at 600 MHz allowed the isomer **47** to be distinguished from **48** with the following isomer distribution: 70% of **47** and 30% of **48**. The constitution for each isomer was determined by 1D NOESY experiments at 600 MHz. Thus, irradiation at the H-4 proton of the indene core in (inden-5-yl)sulfonamide **47** led to a NOE at H-3 and irradiation at the H-7 hydrogen atom gave two observed NOEs, for the methylene protons and H-6, respectively. Concerning (inden-6-yl)sulfonamide **48**, on irradiation at the H-4 proton of the indene core, two NOEs were observed at H-3 and H-5, and irradiation carried out at the H-7 hydrogen atom revealed a NOE for the methylene protons (Fig. 3). Moreover, the COSY experiment of the mixture of isomers **47** and **48** confirmed their constitution (see Supplementary data). The $^1$H NMR data in $CDCl_3$, 1D NOESY and COSY experiments at 500 MHz of the isomeric mixture **49** + **50** showed an isomer distribution of 70% for **49** and 30% for **50**, and the constitution of isomers **49** and **50** could be determined (Fig. 3).

## 3. Results and discussion

Indenes have not yet been extensively explored either from the chemical or biological point of view despite being a source of potential pharmacological ligands, and their synthetic accessibility and suitability for chemical modification is fairly complex.[19]




**Scheme 1.** Reagents and conditions: (a) (i) *N*-methyl-2-pyrrolidinone or *N*-methyl-2-piperidone, LDA, −78 °C, (ii) TFA, $CH_2Cl_2$, 0 °C; (b) (i) $AlH_3$–$NMe_2Et$, THF, 0 °C, (ii) Zn, AcOH, room temperature; (c) $HetSO_2Cl$, pyridine, room temperature.

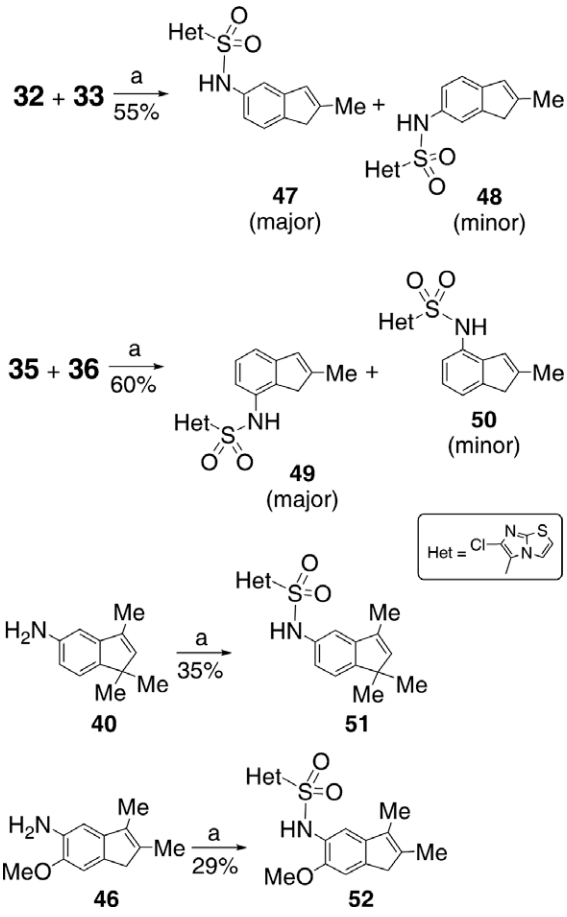


**Scheme 2.** Reagents and conditions: (a) (i) $NaBH_4$, EtOH, room temperature, (ii) 50% $H_2SO_4$, MeOH, 100 °C; (b) (i) EtOAc, LHMDS, THF, −78 °C, (ii) 50% $H_2SO_4$, 60 °C (see Ref. 1); (c) (i) EtOAc, LHMDS, THF, −78 °C, (ii) 50% $H_2SO_4$, 70 °C or 100 °C; (d) Zn, AcOH, room temperature; (e) (i) LDA, THF/DME, −30 °C→−50 °C, (ii) MeI, room temperature; (f) $KNO_3$, 96% $H_2SO_4$, −5 °C.

A few examples of ring-constrained and structurally simplified indenylsulfonamides have been designed and synthesized on the basis of previously established structural requirements for enhancing the affinity of indene-based ligands towards the 5-$HT_6$ receptor, especially the aryl(heteroaryl)sulfonyl portion of the sulfonamide functionality (e.g., the 6-chloroimidazo[2,1-*b*]thiazole structural motif), see Figure S1 in Supplementary data.[1,19] The first synthetic step to the key inden-5-amines **20**, **22** and **25** took advantage of an aldol-type reaction we had previously employed with different indanones, the protocol being adapted to lactams such as *N*-methyl-2-pyrrolidinone or *N*-methyl-2-piperidinone. This initial probe of the two-step sequence to the inden-5-amines **20**, **22** and **25** proceeded with variable yields but in sufficient quantity to follow the synthetic route to the targeted compounds. The new *N*-(inden-5-yl)sulfonamides with a constrained basic side arm at the indene 3-position **26**, **28**–**30** and the structurally abbreviated indene isomeric mixtures **47** + **48** and **49** + **50** as well as compounds **51** and **52** were tested in a standard radioligand competition binding assay,[21,22] using human-cloned 5-$HT_6$ receptors stably expressed by HEK-293 cells and [$^3$H]-lysergic acid diethylamide (LSD) as the radioligand at 37 °C. Only the compounds that demonstrated an inhibition at 100 nM ⩾ 70% were examined for their $K_i$ values (Table 1). Previously reported findings indicate that when the sulfonamide substitution of a 2-naphthyl group is replaced by a heteroaryl group, the $K_i$ decreases.[19] Accordingly, the racemic conformationally constrained *N*-(inden-5-yl)sulfonamides **26**, **28**–**30** showed variable affinities, the highest being observed in the pyrrolidine analog **28** ($K_i$ = 3 nM) with the 3a-azapentalene motif; unfortunately, no biological data is available for pyrrolidine **27** because the 5-$HT_6$ binding assay was not performed. When the restricted amine was a piperidine, compound **30** had a $K_i$ = 18 nM.

Despite lacking the basic amine side chain, the structurally simplified indenylsulfonamides **47** (5-indenyl, 70%) + **48** (6-indenyl, 30%), **51** and **52** exhibited 5-$HT_6$ binding affinities with $K_i$ values in the range of 43–80 nM. When the sulfonamide group was at the indene 7-position, as in the isomeric pairs **49** (7-indenyl, 70%) + **50** (4-indenyl, 30%), the 5-$HT_6$ binding affinity was inappreciable. This had also been observed with **12**-type indenylsulfonamides: moving the sulfonamide group from the 5-position to the 7-position produced a significantly weaker binding affinity and permitted us to rule out additional studies within indene-based frameworks containing the sulfonamide group at the 7-position.[19]

The functional efficacy of indenylsulfonamides **28**, **30**, **47** + **48**, **51** and **52** was evaluated by measuring 5-HT-stimulated cAMP accumulation using HEK-293F cells stably expressing the cloned human 5-$HT_6$ receptor.[9,23,24] In this study, 5-HT-stimulated cAMP accumulation was inhibited with $IC_{50}$ values ∼2 μM. The results indicated that the pyrrolidine indenylsulfonamide **28** was able to block the effect of 5-HT with an $I_{max}$ of 100%, although with modest antagonist potency ($IC_{50}$ = 1.6 μM). Hence, the application of a non-classical bioisosteric indole-to-indene core change led to targeted indenylsulfonamides with high binding affinities although with a significant loss in functional activity. Finally, indenylsulfonamides **28**, **30** and the isomeric mixture **47** + **48** as well as compounds **51** and **52** were further profiled for their selectivity against several serotoninergic and adrenergic receptors as well as the serotonin transporter (SERT), none showing significant activities. Selectivity was maintained even for the structurally fragmented indenylsulfonamides **47** + **48** and **51**, **52** (Table 2). Further insight




**Scheme 3.** Reagents and conditions: (a) 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride, pyridine, room temperature.

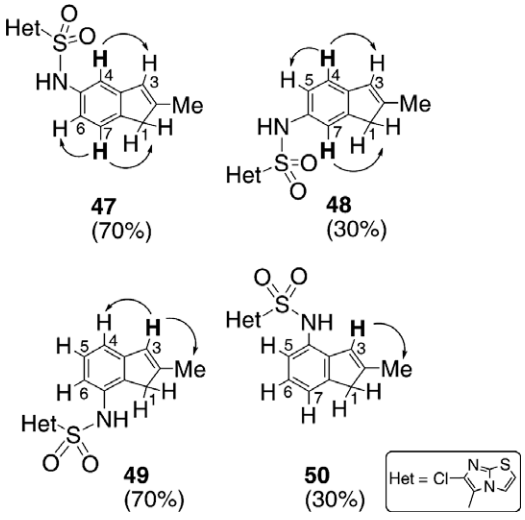
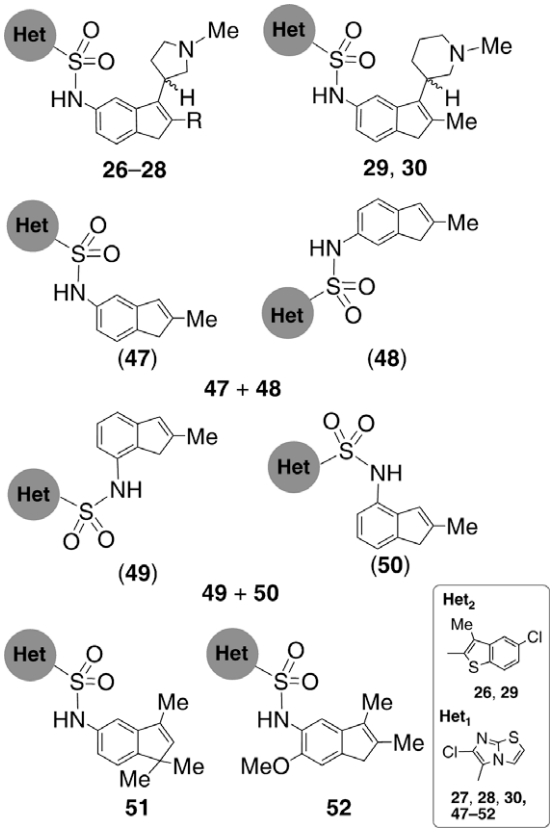



**Figure 3.** Isomer distribution and key NMR responses for the isomeric mixtures of *N*-(indenyl)sulfonamides **47** + **48** and **49** + **50**: 1D NOESY experiments.

into the pharmacophore models for the 5-$HT_6$ receptor could be provided by indenylsulfonamide antagonists **16**-type and **17**-type, which could serve as prototypes to define how the *N*-(inden-5-yl)sulfonamide ligands interact with the 5-$HT_6$ receptor.

**Table 1**
5-$HT_6$ receptor affinity and functionality of compounds **26**–**30** and **47**–**52**



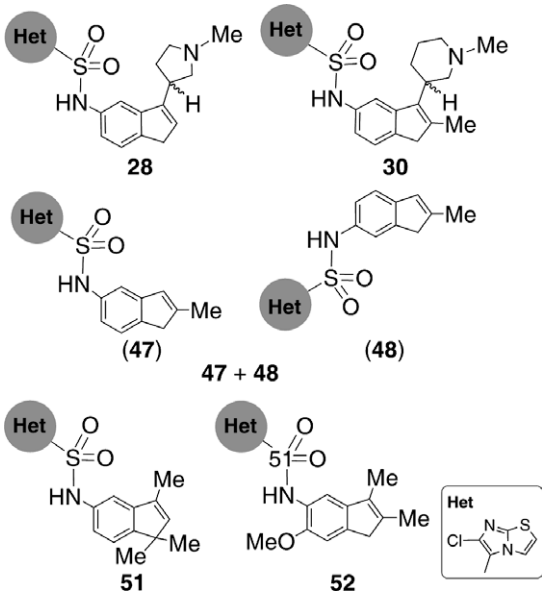

| Compd | R | Het | % Inhib. @ 100 nM | $K_i$[a] (nM) | $I_{max}$[b] (%) | $IC_{50}$[b] (μM) |
|---|---|---|---|---|---|---|
| **26** | Me | $Het_2$ | 57 | | | |
| **27** | Me | $Het_1$ | ND | | | |
| **28** | H | $Het_1$ | 92 | 3.0 | 100 | 1.6 |
| **29** | Me | $Het_2$ | 22 | | | |
| **30** | Me | $Het_1$ | 86 | 18 | 28 | |
| **47** + **48**[c] | Me | $Het_1$ | 78 | 43 | 75 | 3.0 |
| **49** + **50**[d] | Me | $Het_1$ | 5 | | | |
| **51** | H | $Het_1$ | 75 | 80 | 92 | 2.4 |
| **52**[e] | Me | $Het_1$ | 84 | 64 | 10 | |

ND: Not determined.
[a] The 5-$HT_6$ binding assay was performed in triplicate, $K_i$ was calculated when inhib. @ 100 nM >70%.
[b] Antagonism was expressed as $I_{max}$ and $IC_{50}$ values.
[c] Isomer distribution by $^1$H NMR: **47** (5-indenyl) 70% and **48** (6-indenyl) 30%.
[d] Isomer distribution by $^1$H NMR: **49** (7-indenyl) 70% and **50** (4-indenyl) 30%.
[e] Agonism: $E_{max}$ = 49%.

## 4. Conclusions

The ensemble of indene-based frameworks constituted by the *N*-[3-(aminoethyl)inden-5-yl]sulfonamide agonists **12** and the conformationally rigid antagonists **16** as well as the structurally simplified *N*-(inden-5-yl)sulfonamides **17** may be useful pharmacological tools for remodeling the current fundamental understanding of the 5-$HT_6$ receptor. When the basic amine side chain at the indene 3-position was constrained in a five-membered ring, for example, the pyrrolidine analog **28** ($K_i$ = 3 nM), or a six-membered ring, for example, the piperidine analog **30** ($K_i$ = 18 nM), the compounds appeared able to adopt a conformation that permits these high binding affinities for the 5-$HT_6$ receptor. Despite not having an amine side arm, the structurally

**Table 2**
Selectivity over several receptors and serotonin transporter (SERT) of compounds **28**, **30**, **47** + **48**, **51** and **52**




| Compd | $\alpha_1$[a] $IC_{50}$ (nM) | $\alpha_{2A}$[b] $IC_{50}$ (nM) | 5-$HT_{1A}$[c] $IC_{50}$ (nM) | 5-$HT_{2C}$[c] $IC_{50}$ (nM) | SERT[d] $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| **28** | >1000 | 891 | >1000 | 1396 | >10,000 |
| **30** | ND | 1213 | >10,000 | ND | ND |
| **47** + **48** | >10,000 | >10,000 | >10,000 | >1000 | >10,000 |
| **51** | ND | >10,000 | >10,000 | >10,000 | >10,000 |
| **52** | >10,000 | >1000 | >10,000 | >1000 | >10,000 |

ND: Not determined.
[a] Rat $\alpha_1$-adrenoceptor.
[b] Human $\alpha_{2A}$-adrenoceptor.
[c] Human receptor.
[d] Human transporter.

simplified *N*-(inden-5-yl)sulfonamides maintained a binding affinity of $K_i \geqslant 43$ nM. Although these new series of indenylsulfonamides **16** and **17** showed a modest antagonist potency of only $IC_{50}$ ~2 μM, their activities against several serotonergic and adrenergic receptors as well as the serotonin transporter (SERT) were negligible.

## 5. Experimental section

### 5.1. General methods

The reaction yields have not been optimized. All reagents obtained from commercial sources were used without further purification. Melting point: *Gallenkamp Melting Point Apparatus* MPD350.BM2.5 with digital thermometer and are uncorrected. IR (KBr disks or thin film): Nicolet 205 FT or Perkin Elmer 1430 spectrophotometers. $^1$H NMR: Varian Gemini 200 (200 MHz), Varian Gemini 300 (300 MHz), Mercury 400 (400 MHz) and Bruker Avance 600 (600 MHz) spectrometers at 298 K. Chemical shifts were referenced and expressed in ppm ($\delta$) relative to the central peak of DMSO-$d_6$ (2.49 ppm) and TMS for chloroform-*d*. $^{13}$C NMR: Varian Gemini 200 (50.3 MHz), Varian Gemini 300 (75.4 MHz) and Mercury 400 (100.6 MHz) spectrometers at 298 K. Chemical shifts were referenced and expressed in ppm ($\delta$) relative to the central peak of DMSO-$d_6$ (39.7 ppm) and chloroform-*d* (77.0 ppm). 1D double pulsed field gradient spin-echo NOESY: Bruker DMX-500 (500 MHz), Bruker Avance 600 (600 MHz) equipped with a TCI cryoprobe. MS were obtained using EI at 70 eV in a Hewlett-Packard spectrometer (HP-5989A model). Microanalyses were performed on a Carlo Erba 1106 analyzer. ESI-HRMS: Mass spectra were obtained using an Agilent LC/MSD-TOF spectrometer. For the targeted compounds, the chemical purity was determined by HPLC using the following conditions: Waters Alliance 2690 and 2695 (software Millenium 3.20) and Agilent 1100 (software Chemstation A.06.03) equipment with XBridge C18, 3.5 μ, 0.46 × 10 cm column; acetonitrile (ACN)/10 mM ammonium bicarbonate mobile phase, gradient conditions: 0–12 min: from 5% ACN until 95% ACN, 12–17 min: isocratic 95% ACN; flow rate 1 mL/min; temperature 35 °C; $\lambda$ = 210 nm; $t_R$ = 5.4 min. TLC: Merck precoated Silica Gel 60 F254 plates using UV light (254 nm) as a visualizing agent and/or $H_2PtCl_2$ 3% aq/KI 10% aq (1:1) or $KMnO_4$ ethanolic solution. Column chromatography was performed on Silica Gel 60 ACC 35–70 μm Chromagel (SDS).

### 5.2. Materials

*N*-Methyl-2-pyrrolidinone, *N*-methyl-2-piperidone, 5-chloro-3-methyl-1-benzothiophene-2-sulfonyl chloride, 6-chloroimidazo-[2,1-*b*][1,3]thiazole-5-sulfonyl chloride and 5-methoxyindan-1-one **41** are commercial. 2-Methyl-6-nitroindan-1-one **18**,[19] 6-nitroindan-1-one **23**,[19] 6-amino-2-methylindan-1-one **31**,[19] 4-amino-2-methylindan-1-one **34**[19] and 3,3-dimethyl-6-nitroindan-1-one **39**[1] were prepared as previously described.

#### 5.2.1. Synthesis of lactam derivatives 19, 21 and 24. General procedure

To a sufficient amount of dry THF cooled to −78 °C a solution of lithium diisopropylamide (LDA, 1.1 equiv) was added under argon atmosphere. Then, the corresponding lactam (1.05 equiv) was added and the resulting mixture was stirred at −78 °C for 30 min. Finally, a solution of 2-methyl-6-nitroindan-1-one **18** or 6-nitroindan-1-one **23** (1.0 equiv) was added in the sufficient amount of dry THF and the resulting mixture was kept at −78 °C for 2 h. The reaction mixture was acidified with 1 N HCl, the temperature was allowed to rise gradually until reaching room temperature and was extracted with EtOAc. The organic extracts were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. To a stirred solution of the previous residue in dry $CH_2Cl_2$, cooled to 0 °C, was added trifluoroacetic acid (7.0 equiv) and the resulting mixture was stirred at room temperature for 16 h. The organic extracts, after being dried over anhydrous $Na_2SO_4$ and filtered, were evaporated to dryness. The residue obtained was purified by silica gel column chromatography (EtOAc/MeOH as eluent).

**5.2.1.1. *N*-Methyl-3-(2-methyl-5-nitro-1*H*-inden-3-yl)pyrrolidin-2-one 19.** The above procedure was followed using *N*-methyl-2-pyrrolidinone (0.50 mL, 5.49 mmol), LDA (1.5 M in THF, 3.84 mL, 5.75 mmol), 2-methyl-6-nitroindan-1-one **18** (1.0 g, 5.23 mmol) in dry THF (40 mL) and TFA (3 mL) in dry $CH_2Cl_2$ (30 mL). Pyrrolidin-2-one derivate **19** was obtained as a yellow oil (0.25 g, 17%): $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.13–2.23 (m, 4H), 2.36–2.43 (m, 1H), 3.03 (s, 3H), 3.43 (s, 2H), 3.50–3.64 (m, 2H), 3.86 (t, $J$ = 9.9 Hz, 1H), 7.45 (d, $J$ = 8.1 Hz, 1H), 7.82 (d, $J$ = 2.1 Hz, 1H), 8.00 (dd, $J$ = 1.9, 6.0 Hz, 1H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 14.4 ($CH_3$), 24.2 ($CH_2$), 30.2 ($CH_3$), 39.7 (CH), 42.9 ($CH_2$), 47.8 ($CH_2$), 113.1 (CH), 119.4 (CH), 123.4 (CH), 133.8, 145.4, 145.8, 147.2, 149.6, 173.9 (C=O) ppm; IR (thin film): $\nu$(C=O) 1672, $\nu$($NO_2$) 1524, 1342 cm$^{-1}$; MS (EI, 70 eV) *m/z* (%): 272 (34) [$M^{+\cdot}$], 255 (100) [$M^{+\cdot}-17$].

**5.2.1.2. *N*-Methyl-3-(2-methyl-5-nitro-1*H*-inden-3-yl)piperidin-2-one 21.** The above procedure was followed using *N*-methyl-2-piperidone (0.50 mL, 4.56 mmol), LDA (1.5 M in THF, 3.18 mL, 4.77 mmol), 2-methyl-6-nitroindan-1-one **18** (0.83 g, 4.34 mmol) in dry THF (20 mL) and TFA (4 mL) in dry $CH_2Cl_2$ (50 mL). Piperidin-2-one derivate **21** was obtained as a yellow oil (0.57 g, 46%): $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.95–2.04 (m, 4H), 2.11 (s, 3H), 3.10 (s, 3H), 3.42 (d, $J$ = 4.2 Hz, 2H), 3.50 (m, 1H), 3.63–3.67 (m, 1H), 3.72–3.77 (m, 1H), 7.44 (d, $J$ = 8.4 Hz, 1H), 7.77 (d, $J$ = 2.1 Hz, 1H), 8.00 (dd, $J$ = 2.3, 8.1 Hz, 1H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 14.3 ($CH_3$), 22.6 ($CH_2$), 27.6 ($CH_2$), 35.1 ($CH_3$), 40.4 (CH), 42.9 ($CH_2$), 50.4 ($CH_2$), 113.3 (CH), 119.2 (CH), 123.3 (CH), 136.1, 143.6, 146.3, 147.2, 149.7, 169.4 (C=O) ppm; IR (thin film): $\nu$(C=O) 1637, $\nu$($NO_2$) 1505, 1340 cm$^{-1}$; MS (EI, 70 eV) *m/z* (%): 286 (58) [$M^{+\cdot}$], 269 (100) [$M^{+\cdot}-17$].

**5.2.1.3. *N*-Methyl-3-(5-nitro-1*H*-inden-3-yl)pyrrolidin-2-one 24.** The above procedure was followed using *N*-methyl-2-pyrrolidinone (1.14 mL, 11.85 mmol), LDA (1.5 M in THF, 8.28 mL, 12.42 mmol), 6-nitroindan-1-one **23** (2.0 g, 11.29 mmol) in dry THF (60 mL) and TFA (5 mL) in dry $CH_2Cl_2$ (100 mL). Pyrrolidin-2-one derivate **24** was obtained as a brown solid (0.45 g, 15%): mp 87–88 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.10–2.23 (m, 1H), 2.50–2.62 (m, 1H), 2.98 (s, 3H), 3.49–3.59 (m, 4H), 3.81 (t, $J$ = 8.7 Hz, 1H), 6.58 (d, $J$ = 0.9 Hz, 1H), 7.55 (dd, $J$ = 0.6, 8.1 Hz, 1H), 7.54–7.57 (m, 1H), 8.11 (dd, $J$ = 1.9, 8.2 Hz, 1H), 8.18 (d, $J$ = 2.1 Hz, 1H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 25.0 ($CH_2$), 30.0 ($CH_3$), 38.1 ($CH_2$), 41.3 (CH), 47.6 ($CH_2$), 114.5 (CH), 120.3 (CH), 124.0 (CH), 132.7 (CH), 141.4, 145.3, 147.3, 151.4, 173.4 (C=O) ppm; IR (KBr): $\nu$(C=O) 1670, $\nu$($NO_2$) 1521, 1345 cm$^{-1}$; MS (EI, 70 eV) *m/z* (%): 258 (100) [$M^{+\cdot}$], 154 (46) [$M^{+\cdot}-104$].

#### 5.2.2. Synthesis of inden-5-amines 20, 22 and 25. General procedure

To a sufficient amount of dry THF cooled to 0 °C, alane-*N*,*N*-dimethylethylamine complex ($AlH_3$–$NMe_2Et$, 1.6 equiv) was added under argon atmosphere. Then, a solution of lactam derivatives **19**, 21 or **24** (1.0 equiv) in dry THF cooled to 0 °C was added. At the end of the addition, the mixture was maintained at the same temperature for 30 min. THF/$H_2O$ (1:1) and EtOAc were added slowly to the reaction mixture and the temperature was allowed to rise slowly to room temperature. The resulting suspension was filtered through Celite. The layers were separated and the organic extract was washed with brine, dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. To a solution of the previous residue in glacial AcOH, zinc (10–20 equiv) was added in portions. The resulting suspension was stirred at room temperature (3–16 h). The reaction mixture was filtered through Celite and the filtered liquid was evaporated to dryness. The residue obtained was dissolved in EtOAc and washed with saturated $Na_2CO_3$ aqueous solution. The organic extract, after being dried over anhydrous $Na_2SO_4$ and filtered, was evaporated to dryness.

**5.2.2.1. 2-Methyl-3-(1-methylpyrrolidin-3-yl)-1*H*-inden-5-amine 20.** The above procedure was followed using pyrrolin-2-one derivative **19** (0.32 g, 1.18 mmol) and $AlH_3$–$NMe_2Et$ (0.5 M in toluene, 3.80 mL, 1.89 mmol) in dry THF (20 mL) and zinc (0.46 g, 7.1 mmol) in glacial AcOH (5 mL). Inden-5-amine **20** was obtained as an orange foamy solid (0.12 g, 44%): $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.05–2.10 (m, 5H), 2.43 (s, 3H), 2.70–2.80 (m, 5H), 3.16 (s, 2H), 6.46 (dd, $J$ = 1.9, 8.1 Hz, 1H), 6.97 (d, $J$ = 2.1 Hz, 1H), 7.13 (d, $J$ = 7.8 Hz, 1H) ppm; HRMS-ESI *m/z* [M+H]$^+$ calcd for $C_{15}H_{20}N_2$: 229.1699; found: 229.1698.

**5.2.2.2. 2-Methyl-3-(1-methylpiperidin-3-yl)-1*H*-inden-5-amine 22.** The above procedure was followed using piperidin-2-one derivative **21** (0.29 g, 1.03 mmol) and $AlH_3$–$NMe_2Et$ (0.5 M in toluene, 3.31 mL, 1.65 mmol) in dry THF (15 mL) and zinc (1.6 g, 24.81 mmol) in glacial AcOH (10 mL). Inden-5-amine **22** was obtained as a dark foamy solid (0.21 g, 85%): mp 254–255 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.70–1.88 (m, 7H), 1.98–2.04 (m, 2H), 2.14–2.34 (m, 5H), 3.17 (s, 2H), 6.45 (dd, $J$ = 2.1, 7.8 Hz, 1H), 6.84 (d, $J$ = 2.1 Hz, 1H), 7.11 (dd, $J$ = 0.6, 7.8 Hz, 1H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 14.8 ($CH_3$), 26.2 ($CH_2$), 27.8 ($CH_2$), 36.5 (CH), 42.5 ($CH_2$), 46.6 ($CH_3$), 56.1 ($CH_2$), 59.4 ($CH_2$), 107.5 (CH), 110.6 (CH), 123.6 (CH), 133.1, 137.9, 140.4, 144.5, 146.9 ppm; IR (KBr): $\nu$($NH_2$) 3369 cm$^{-1}$; MS (EI, 70 eV) *m/z* (%): 242 (31) [$M^{+\cdot}$], 145 (26) [$M^{+\cdot}-97$], 58 (100) [$M^{+\cdot}-184$]. Anal. Calcd for $C_{16}H_{22}N_2O_2S_2\cdot 0.13H_2O$: C, 78.73; H, 9.17; N, 11.45. Found: C, 78.60; H, 9.13; N, 11.60.

**5.2.2.3. 3-(1-Methylpyrrolidin-3-yl)-1*H*-inden-5-amine 25.** The above procedure was followed using pyrrolidin-2-one derivative **24** (0.43 g, 1.66 mmol) and $AlH_3$–$NMe_2Et$ (0.5 M in toluene, 5.33 mL, 2.66 mmol) in dry THF (25 mL) and zinc (1.0 g, 15.3 mmol) in glacial AcOH (30 mL). Inden-5-amine **25** was obtained as a brown oil (60.0 mg, 17%): $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.88–2.00 (m, 1H), 2.19–2.37 (m, 1H), 2.40 (s, 3H), 2.50–2.61 (m, 2H), 2.73–2.81 (m, 2H), 2.97–3.03 (m, 1H), 3.23 (s, 2H), 6.23 (d, $J$ = 1.5 Hz, 1H), 6.54 (dd, $J$ = 2.1, 7.8 Hz, 1H), 6.75 (d, $J$ = 2.1 Hz, 1H), 7.20 (dd, $J$ = 0.6, 7.8 Hz, 1H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 30.5 ($CH_2$), 36.8 (CH), 42.3 ($CH_3$), 56.2 ($CH_2$), 61.1 ($CH_2$), 106.8 (CH), 111.9 (CH), 124.0 (CH), 127.2 (CH), 134.9, 144.8, 146.1, 146.6 ppm; HRMS-ESI *m/z* [M+H]$^+$ calcd for $C_{14}H_{19}N_2$: 215.1542; found: 215.1542.

#### 5.2.3. Synthesis of indenamines 32–33 and 35–36. General procedure

To a stirred solution of 6-amino-2-methylindan-1-one **31** or 4-amino-2-methylindan-1one **34** (1.0 equiv) in absolute EtOH cooled to 0 °C, $NaBH_4$ (1.5 equiv) was added under argon atmosphere. After stirring at room temperature (4–19 h), water was added to the reaction mixture and was extracted with $CH_2Cl_2$. The organic extracts were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. A solution of the previous residue in the sufficient amount of MeOH was added to a 50% $H_2SO_4$ aqueous solution and stirred at room temperature for 18 h. The reaction mixture was diluted in water, basified with $Na_2CO_3$ and extracted with $CH_2Cl_2$. The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness.

**5.2.3.1. 2-Methyl-1*H*-inden-5-amine 32 and2-methyl-1*H*-inden-6-amine 33.** The above procedure was followed using 6-amino-2-methylindan-1-one **31** (0.50 g, 3.10 mmol) in absolute EtOH (35.0 mL), $NaBH_4$ (176.0 mg, 4.65 mmol) and 50% $H_2SO_4$ aqueous solution (20.0 mL). A mixture of isomeric inden-5-amines **32** and **33** was obtained as a yellow solid (0.40 g, 90%): mp 66–67 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.10 (s, 3H, minor), 2.12 (s, 3H, major), 3.20 (s, 4H, major and minor), 3.56 (br s, 2H), 6.36–6.37 (m, 1H, major), 6.45 (dd, *J* = 2.4, 7.8 Hz, 1H, major), 6.56 (dd, *J* = 2.4, 7.8 Hz, 1H, minor), 6.62 (d, *J* = 2.1 Hz, 1H, major), 6.78 (m, 1H, minor), 7.02 (d, *J* = 7.8 Hz, 1H, minor), 7.12 (d, *J* = 7.8 Hz, 1H, major) ppm; $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ = 16.6 ($CH_3$, minor), 16.8 ($CH_3$, major), 41.9 ($CH_2$, major), 42.5 ($CH_2$, minor), 107.2 (CH, major), 110.6 (CH, major), 111.6 (CH, minor), 113.1 (CH, minor), 119.8 (CH, minor), 123.5 (CH, major), 126.9 (CH, major), 133.6 (major), 137.4 (minor), 142.0 (minor), 142.9 (minor), 144.9 (major), 145.1 (minor), 147.1 (major), 147.2 (major) ppm; IR (KBr): $\nu$($NH_2$) 3395 $cm^{-1}$. MS (EI, 70 eV) *m/z* (%): 145 (100) [$M^{+\cdot}$], 130 (79) [$M^{+\cdot}-15$].

**5.2.3.2. 2-Methyl-1*H*-inden-7-amine 35 and 2-methyl-1*H*-inden-4-amine 36.** The above procedure was followed using 4-amino-2-methylindan-1-one **34** (0.25 g, 1.55 mmol) in absolute EtOH (20 mL), $NaBH_4$ (88.0 mg, 2.33 mmol) and 50% $H_2SO_4$ aqueous solution (10.0 mL). A mixture of isomeric inden-7-amines **35** and **36** was obtained as a dark orange oil (179.0 mg, 80%): $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.16 (s, 6H, major and minor), 3.10 (s, 4H, major and minor), 3.59–3.60 (br s, 2H), 6.45–6.51 (m, 4H, major and minor), 6.77 (d, *J* = 7.5 Hz, 2H, major and minor), 7.07 (t, *J* = 7.7 Hz, 2H, major and minor) ppm. $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 16.8 ($CH_3$, major and minor), 39.7 ($CH_2$, major and minor), 111.4 (CH, major and minor), 126.9 (major and minor), 127.6 (CH, major and minor), 127.7 (CH, major and minor), 141.0 (major and minor), 145.0 (major and minor), 146.8 (major and minor) ppm; IR (KBr): $\nu$($NH_2$) 3273 $cm^{-1}$.

#### 5.2.4. (1,1-Dimethyl-5-nitro-1*H*-inden-3-yl)acetic acid 38 and 1,1,3-trimethyl-5-nitro-1*H*-indene 39

To dry THF (2 mL) cooled to −78 °C, a solution of LHMDS (1.0 M in THF, 2.68 mL, 2.68 mmol) was added under argon atmosphere. Then, dry EtOAc (0.25 mL, 2.56 mmol) was added and the resulting mixture was stirred at −78 °C for 30 min. Finally, a solution 3,3-dimethyl-6-nitroindan-1-one **37** (0.50 g, 2.44 mmol) in dry THF (12 mL) was added and the resulting mixture was stirred at −78 °C for 2 h. The reaction mixture was acidified with 1 N HCl, the temperature was allowed to rise gradually until reaching room temperature and was extracted with EtOAc (3 × 30 mL). The organic extracts were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. To the previous residue was added a 50% $H_2SO_4$ aqueous solution (15 mL) and was heated to 70 °C for 5 h. The reaction mixture was washed with saturated $Na_2CO_3$ aqueous solution (3 × 50 mL). The organic extract after being dried over anhydrous $Na_2SO_4$ and filtered, were evaporated to dryness to give the indene derivative **39** as a brown solid (78.0 mg, 16%). The aqueous extracts were acidified with 37% HCl solution and were extracted with $CH_2Cl_2$ (3 × 50 mL). The organic extracts after being dried over anhydrous $Na_2SO_4$ and filtered, were evaporated to dryness to give indenylacetic acid **38** (0.12 g, 20%) as a white solid. The spectral data of **38** were identical to those previously reported.

*Compound* 39: mp 81–82 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.32 (s, 6H), 2.14 (s, 3H), 6.19–6.20 (m, 1H), 7.39 (dd, *J* = 0.6, 8.4 Hz, 1H), 8.04 (d, *J* = 2.1 Hz, 1H), 8.09–8.12 (m, 1H) ppm; $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ = 12.6 ($CH_3$), 24.2 ($CH_3$), 48.6, 114.2 (CH), 120.8 (CH), 121.2 (CH), 123.4, 134.7, 144.7 (CH), 145.5, 160.9 ppm; IR (KBr): $\nu$($NO_2$) 1519, 1343 $cm^{-1}$; HRMS-ESI $[M+H]^+$ calcd for $C_{12}H_{13}NO_2$: 204.1019, found: 204.1020.

#### 5.2.5. 5-Methoxy-2-methylindan-1-one 42

To a stirred solution of 5-methoxyindan-1-one **41** (2.0 g, 12.33 mmol) in dry THF/dimethoxyethane (4:1, 120.0 mL) was added LDA (1.50 M in THF, 9.0 mL, 13.56 mmol) at −30 °C under argon atmosphere. After stirring for 1.5 h at −50 °C, MeI (3.80 mL, 61.65 mmol) was added and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was added to water and extracted with EtOAc (3 × 300 mL). The organic extracts were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The residue obtained was purified by silica gel column chromatography (hexanes/EtOAc as eluent). Indanone **42** was obtained as a white solid (1.05 g, 50%): mp 60–61 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.45 (dd, *J* = 1.8, 7.5 Hz, 3H), 2.80–2.88 (m, 2H), 3.48–3.55 (m, 1H), 4.04 (s, 3H), 7.04–7.08 (m, 2H), 7.84 (d, *J* = 8.1 Hz, 1H) ppm. $^{13}$C NMR (75.4 MHz, $CDCl_3$,): $\delta$ = 16.5 ($CH_3$), 35.0 ($CH_2$), 42.1 (CH), 55.6 ($CH_3$), 109.6 (CH), 115.2 (CH), 125.5 (CH), 129.5, 156.4, 165.2, 207.6 (C=O) ppm; IR (KBr): $\nu$($OCH_3$) 2842, 1252; $\nu$(C=O) 1701 $cm^{-1}$; MS (EI, 70 eV) *m/z* (%): 176 (53) [$M^{+\cdot}$], 161 (100) [$M^{+\cdot}-15$].

#### 5.2.6. 5-Methoxy-2-methyl-6-nitroindan-1-one 43 and 5-methoxy-2-methyl-4-nitroindan-1-one 44

To 96% $H_2SO_4$ aqueous solution (6.0 mL), cooled to 0 °C, was added in one portion 5-methoxy-2-methylindan-1-one **42** (1.0 g, 5.67 mmol). Then, a solution of $KNO_3$ (0.60 g, 6.38 mmol) in 96% $H_2SO_4$ aqueous solution (6.0 mL) was added dropwise. After stirring for 1 h at −5 °C, the reaction mixture was poured over ice (500 mL), was stirred at room temperature and extracted with $CH_2Cl_2$ (3 × 100 mL). The organic extracts were washed with $Na_2CO_3$ saturated aqueous solution (3 × 50 mL), dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The residue obtained was purified by silica gel column chromatography (hexanes/EtOAc as eluent). Nitroindanone **43** (0.26 g, 20%) was obtained as a yellow solid and nitroindanone **44** was obtained as a white solid (0.80 g, 63%).

*Compound* **43**: mp 108–109 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.31–1.33 (m, 3H), 2.73–2.81 (m, 2H), 3.44 (dd, *J* = 6.8, 14.0 Hz, 1H), 7.09 (s, 1H), 8.17 (s, 1H) ppm; $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ = 16.3 ($CH_3$), 35.2 ($CH_2$), 42.3 (CH), 56.9 ($CH_3$), 110.1 (CH), 121.5 (CH), 128.6, 157.5, 159.0, 206.0 (C=O) ppm. IR (KBr): $\nu$($OCH_3$) 2872, 1299, $\nu$(C=O) 1715; $\nu$($NO_2$) 1611, 1359 $cm^{-1}$; MS (EI, 70 eV) *m/z* (%): 221 (87) [$M^{+\cdot}$], 206 (38) [$M^{+\cdot}-15$].

*Compound* 44: mp 119–120 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.31 (d, *J* = 7.5 Hz, 3H), 2.73–2.87 (m, 2H), 3.43–3.52 (m, 1H), 4.02 (s, 3H), 7.12 (d, *J* = 8.7 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ 16.2 ($CH_3$), 32.9 ($CH_2$), 41.9 (CH), 57.1 ($CH_3$), 112.8 (CH), 128.5 (CH), 130.1, 148.2, 156.9, 205.7 (C=O) ppm; IR (KBr): $\nu$($OCH_3$) 2874, 1259; $\nu$(C=O) 1713, $\nu$($NO_2$)

1612, 1363 $cm^{-1}$; MS (EI, 70 eV) *m/z* (%): 221 (100) [$M^{+\cdot}$], 204 (38) [$M^{+\cdot}-17$].

#### 5.2.7. 2,3-Dimethyl-5-nitro-1*H*-inden-6-yl methyl ether 45

To dry THF (5.0 mL) cooled to −78 °C, a solution of LHMDS (1.0 M in THF, 1.10 mL, 1.19 mmol) was added under argon atmosphere. Then, dry EtOAc (0.12 mL, 1.19 mmol) was added and the resulting mixture was stirred at −78 °C for 30 min. Finally, a solution of nitroindanone **43** (0.24 g, 1.08 mmol) in dry THF (15.0 mL) was added and the resulting mixture was stirred at −78 °C for 2 h. The reaction mixture was acidified with 1 N HCl, the temperature was allowed to rise gradually until reaching room temperature and was extracted with EtOAc (3 × 50 mL). The organic extracts were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The previous residue was added to a 50% $H_2SO_4$ aqueous solution (20.0 mL) cooled to −5 °C and was heated to 100 °C for 4 h. Water (50 mL) was added to the reaction mixture and was extracted with EtOAc (3 × 50 mL). The organic extracts, after being dried over anhydrous $Na_2SO_4$ and filtered, were evaporated to dryness. The residue obtained was purified by silica gel column chromatography (hexanes/EtOAc as eluent). Indene derivative **45** was obtained as a yellow solid (0.12 g, 51%): mp 155–156 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.02 (s, 3H), 2.05 (s, 3H), 3.32 (s, 2H), 3.97 (s, 3H), 7.13 (s, 1H), 7.64 (s, 1H) ppm; $^{13}$C NMR (50.3 MHz, $CDCl_3$): $\delta$ = 10.1 ($CH_3$), 13.9 ($CH_3$), 42.8 ($CH_2$), 56.8 ($CH_3$), 109.1 (CH), 114.2 (CH), 131.2, 138.5, 140.3, 149.3, 150.8 ppm; IR (KBr): $\nu$($OCH_3$) 2915, 1268, $\nu$($NO_2$) 1512, 1339 $cm^{-1}$; MS (EI, 70 eV) *m/z* (%): 219 (100) [$M^{+\cdot}$], 128 (59) [$M^{+\cdot}-91$].

#### 5.2.8. Synthesis of 3-methyl-1*H*-inden-5-amines 40 and 46. General procedure

To a solution of 1,1,3-trimethyl-5-nitro-1*H*-indene **39** or 2,3-dimethyl-5-nitro-1*H*-inden-6-yl methyl ether **45** (1.0 equiv) in glacial AcOH, zinc (25.0 equiv) was added in portions. The resulting suspension was stirred at room temperature for 4.5 h. The reaction mixture was filtered through Celite and the filtered liquid was evaporated to dryness. The residue obtained was dissolved in $CH_2Cl_2$ and washed with 10% $NaHCO_3$ aqueous solution. The organic extract, after being dried over anhydrous $Na_2SO_4$ and filtered, was evaporated to dryness.

**5.2.8.1. 1,1,3-Trimethyl-1*H*-inden-5-amine 40.** The above procedure was followed using 1,1,3-trimethyl-5-nitro-1*H*-indene **39** (0.30 mg, 1.48 mmol) and zinc (2.41 g, 36.9 mmol) in glacial AcOH (15.0 mL). Inden-5-amine **40** was obtained as a brown solid (0.20 g, 80%): $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.25 (s, 9H), 3.60 (br s, 2H), 6.00 (d, *J* = 1.5 Hz, 1H), 6.58 (d, *J* = 1.8 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H) ppm.

**5.2.8.2. 6-Methoxy-2,3-dimethyl-1*H*-inden-5-amine 46.** The above procedure was followed using 2,3-dimethyl-5-nitro-1*H*-inden-6-yl methyl ether **45** (0.10 g, 0.46 mmol) and zinc (0.75 g, 11.4 mmol) in glacial AcOH (5.0 mL). Inden-5-amine **46** was obtained as a brown solid (84.0 mg, 97%): $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.96 (s, 3H), 2.01 (s, 3H), 3.17 (s, 2H), 3.86 (s, 3H), 6.62 (s, 1H), 6.90 (s, 1H) ppm.

#### 5.2.9. Synthesis of inden-5-ylsulfonamides 26–30, 47–52. General procedure

To a stirred solution of indenamines **20**, **22**, **25**, **32–33**, **35–36**, **40** or **46** (1.0 equiv) in dry pyridine was added dropwise a solution of the corresponding sulfonyl chloride (1.0–1.1 equiv) in dry pyridine. The resulting mixture was stirred at room temperature (6–23 h). The reaction mixture was evaporated to dryness. The residue obtained was purified by silica gel column chromatography ($CH_2Cl_2$/$NH_3$/MeOH as eluent).

**5.2.9.1. 5-Chloro-3-methyl-*N*-[2-methyl-3-(1-methylpyrrolidin-3-yl)-1*H*-inden-5-yl]benzo[b]thiophene- 2-sulfonamide 26.** The above procedure was followed using inden-5-amine **20** (0.11 g, 0.48 mmol) and 5-chloro-3-methyl-1-benzothiophene-2-sulfonyl chloride (0.17 g, 0.61 mmol) in dry pyridine (2.5 mL). Indenylsulfonamide **26** was obtained as a yellow solid (41.0 mg, 18%): mp 220–221 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.78–1.95 (m, 2H), 2.04 (s, 2H), 2.32 (s, 3H), 2.35 (s, 3H), 2.47–2.82 (m, 4H), 3.19 (s, 2H), 3.49 (t, *J* = 9.0 Hz, 1H), 6.97 (dd, *J* = 1.9, 8.1 Hz, 1H), 7.10 (d, *J* = 2.1 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.40 (dd, *J* = 2.1, 9.0 Hz, 1H), 7.66–7.72 (m, 2H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 11.6 ($CH_3$), 14.0 ($CH_3$), 28.8 ($CH_2$), 35.4 (CH), 41.8 ($CH_3$), 42.2 ($CH_2$), 56.4 ($CH_2$), 58.8 ($CH_2$), 114.3 (CH), 118.5 (CH), 123.0 (CH), 123.4 (CH), 123.5 (CH), 127.4 (CH), 131.1, 133.9, 136.1, 136.3, 137.4, 140.4, 140.5, 141.1, 145.2 ppm; IR (KBr): $\nu$($SO_2$) 1325, 1156 $cm^{-1}$; HRMS-ESI *m/z* [M+H]$^+$ calcd for $C_{24}H_{26}N_2O_2S_2Cl$: 437.1119, found: 437.1118.

**5.2.9.2. 6-Chloro-*N*-[2-methyl-3-(1-methylpyrrolidin-3-yl)-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 27.** The above procedure was followed using inden-5-amine **20** (80.0 mg, 0.35 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.10 g, 0.38 mmol) in dry pyridine (4.0 mL). Indenylsulfonamide **27** was obtained as a brown oil (18.0 mg, 11%): $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.02–2.04 (s, 5H), 2.53 (s, 3H), 2.63–3.00 (m, 4H), 3.17 (s, 2H), 3.57 (t, *J* = 8.7 Hz, 1H), 6.85 (d, *J* = 4.8 Hz, 1H), 7.03 (dd, *J* = 1.9, 7.5 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 1.8 Hz, 1H), 7.77 (d, *J* = 6.0 Hz, 1H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 14.2 ($CH_3$), 29.7 ($CH_2$), 35.4 (CH), 42.1 ($CH_3$), 42.3 ($CH_2$), 56.9 ($CH_2$), 58.8 ($CH_2$), 113.6 (CH), 115.2 (CH), 118.7 (CH), 118.9, 120.5 (CH), 123.7 (CH), 134.1, 136.6, 137.3, 140.7, 141.3, 145.4, 149.3 ppm; IR (thin film): $\nu$(NH) 3394; $\nu$($SO_2$) 1332, 1144 $cm^{-1}$; HRMS-ESI *m/z* [M+H]$^+$ calcd for $C_{20}H_{22}N_4O_2S_2Cl$: 449.0867, found: 449.0877.

**5.2.9.3. 6-Chloro-*N*-[3-(1-methylpyrrolidin-3-yl)-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 28.** The above procedure was followed using inden-5-amine **25** (60.0 mg, 0.28 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (72.0 mg, 0.28 mmol) in dry pyridine (3.0 mL). Indenylsulfonamide **28** was obtained as an off-white solid (33.0 mg, 27%): mp 193–194 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.81–1.90 (m, 1H), 2.20–232 (m, 1H), 2.54 (s, 3H), 2.57–2.74 (m, 2H), 2.92–3.00 (m, 1H), 3.12–3.18 (m, 1H), 3.23 (s, 2H), 3.33–3.38 (m, 1H), 5.33 (br s, 1H), 6.23 (s, 1H), 6.86 (d, *J* = 4.5 Hz, 1H), 7.03–7.09 (m, 2H), 7.25–7.28 (m, 1H), 7.73 (d, *J* = 4.5 Hz, 1H) ppm; $^{13}$C NMR (75.4 MHz DMSO-$d_6$): $\delta$ = 29.71 ($CH_2$), 36.1 ($CH_2$), 36.6 (CH), 41.6 ($CH_3$),55.4 ($CH_2$), 60.0 ($CH_2$), 112.1 (CH), 116.5 (CH), 116.6 (CH), 118.0 (CH), 118.6, 119.9 (CH), 124.1 (CH), 128.2 (CH), 135.9, 136.1, 140.3, 145.3, 145.5, 149.1 ppm; IR (KBr): $\nu$(NH) 3128, $\nu$($SO_2$) 1270, 1116 $cm^{-1}$; HRMS-ESI *m/z* [M+H]$^+$ calcd for $C_{19}H_{20}N_4O_2S_2Cl$: 435.0711, found: 435.0708.

**5.2.9.4. 5-Chloro-3-methyl-*N*-[2-methyl-3-(1-methylpiperidin-3-yl)-1*H*-inden-5-yl]benzo[b]thiophene- 2-sulfonamide 29.** The above procedure was followed using inden-5-amine **22** (0.35 g, 1.45 mmol) and 5-chloro-3-methyl-1-benzothiophene-2-sulfonyl chloride (0.50 g, 1.78 mmol) in dry pyridine (3.5 mL). Indenylsulfonamide **29** was obtained as an off-white solid (0.12 g, 17%): mp 213–214 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.57–1.68 (m, 4H), 2.04–2.07 (m, 5H), 2.27 (s, 3H), 2.35 (s, 3H), 2.73 (dd, *J* = 3.1, 11.7 Hz, 1H), 2.97 (d, *J* = 11.7 Hz, 2H), 3.19 (s, 2H), 6.97 (dd, *J* = 1.9, 8.1 Hz, 1H), 7.04 (d, *J* = 1.8 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.39 (dd, *J* = 1.9, 8.7 Hz, 1H), 7.67–7.71 (m, 2H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 11.7 ($CH_3$), 14.5 ($CH_3$), 25.1 ($CH_2$), 27.0 ($CH_2$), 35.3 (CH), 42.7 ($CH_2$), 45.5 ($CH_3$), 55.4 ($CH_2$), 58.4 ($CH_2$), 113.9 (CH), 118.1 (CH), 123.0 (CH), 123.4 (CH), 123.5 (CH), 127.4 (CH), 131.1, 134.1, 136.4, 136.6, 137.5,

140.1, 140.5, 141.1, 146.3 ppm; IR (KBr): $\nu$(NH) 3432; $\nu(SO_2)$ 1321, 1151 $cm^{-1}$; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{25}H_{28}N_2O_2SCl$: 487.1275, found: 487.1276.

**5.2.9.5. 6-Chloro-*N*-[2-methyl-3-(1-methylpiperidin-3-yl)-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 30.** The above procedure was followed using inden-5-amine **22** (0.21 g, 0.88 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.23 g, 0.88 mmol) in dry pyridine (5.0 mL). Indenylsulfonamide **30** was obtained as an off-white foamy solid (73.0 mg, 18%): mp 210–211 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.62–1.78 (m, 4H), 1.99–2.05 (m, 5H), 2.30 (s, 2H), 2.36 (s, 3H), 2.74 (d, *J* = 2.7 Hz, 2H), 2.77–2.78 (m, 2H), 2.96–3.00 (m, 2H), 3.17 (s, 2H), 6.88 (d, *J* = 4.2 Hz, 1H), 6.91 (dd, *J* = 2.1, 7.8 Hz, 1H), 7.18–7.21 (m, 2H), 7.72 (d, *J* = 4.5 Hz, 1H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 14.7 ($CH_3$), 25.8 ($CH_2$), 27.5 ($CH_2$), 36.1 (CH), 42.7 ($CH_2$), 46.4 ($CH_3$), 55.9 ($CH_2$), 58.9 ($CH_2$), 113.8 (CH), 15.5 (CH), 118.7, 119.0 (CH), 120.4 (CH), 123.8 (CH), 133.2, 137.3, 137.6, 141.3, 141.4, 146.9 ppm; IR (KBr): $\nu$(NH) 3118, $\nu(SO_2)$ 1337, 1142 $cm^{-1}$. Anal. Calcd for $C_{21}H_{23}ClN_4O_2S_2{\cdot}0.3H_2O$: C, 53.85; H, 5.08; N, 11.96; S, 13.69. Found: C, 53.50; H, 5.04; N, 11.80; S, 13.73.

**5.2.9.6. 6-Chloro-*N*-(2-methyl-1*H*-inden-5-yl)imidazo[2,1-*b*][1,3]-thiazole-5-sulfonamide 47 and 6-chloro-*N*-(2-methyl-1*H*-inden-6-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 48.** The above procedure was followed using a mixture of isomeric inden-5-amines **32** and **33** (0.20 g, 1.38 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.35 g, 1.38 mmol) in dry pyridine (8.0 mL). A mixture of isomeric indenylsulfonamides **47** and **48** was obtained as a salmon foamy solid in a 7:3 ratio (0.28 g, 55%): mp 146–147 °C; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 2.09 (s, 6H, major and minor), 3.18 (s, 4H, major and minor), 6.34 (s, 1H, major), 6.36 (s, 1H, minor), 6.79 (dd, *J* = 2.1, 7.9 Hz, 1H, major), 6.85 (d, *J* = 4.5 Hz, 1H, minor), 6.87 (d, *J* = 4.5 Hz, 1H, major), 6.90 (br s, 2H, major and minor), 6.93 (dd, *J* = 2.0, 8.0 Hz, 1H, minor), 7.00 (d, *J* = 2.0 Hz, 1H, major), 7.04 (d, *J* = 8.0 Hz, 1H, minor), 7.12 (br s, 1H, minor), 7.15 (d, *J* = 7.9 Hz, 1H, major), 7.60 (d, *J* = 4.5 Hz, 1H, minor), 7.66 (d, *J* = 4.5 Hz, 1H, major) ppm; $^{13}$C NMR (75.4 MHz, DMSO-$d_6$): $\delta$ = 16.5 ($CH_3$), 41.7 ($CH_2$), 42.2 ($CH_2$), 112.3 (CH), 116.1 (CH), 116.8 (CH), 117.8 (CH), 119.6 (CH), 119.8 (CH), 123.6 (CH), 126.0 (CH), 126.3 (CH), 132.0, 134.6, 136.7, 139.8, 142.8, 144.1, 146.4, 148.1, 149.5 ppm; IR (KBr): $\nu$(NH) 3125, $\nu(SO_2)$ 1251, 1145 $cm^{-1}$; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{15}H_{13}N3O_2S_2Cl$: 366.0132, found: 366.0138.

**5.2.9.7. 6-Chloro-*N*-(2-methyl-1*H*-inden-7-yl)imidazo[2,1-*b*]-[1,3]thiazole-5-sulfonamide 49 and 6-chloro-*N*-(2-methyl-1*H*-inden-4-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 50.** The above procedure was followed using a mixture of isomeric inden-5-amines **35** and **36** (0.15 g, 1.03 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.27 g, 1.03 mmol) in dry pyridine (6.5 mL). A mixture of isomeric indenylsulfonamides **49** and **50** was obtained as a yellow foamy solid (0.22 g, 60%): mp 149–150 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 2.09 (s, 3H, minor), 2.14 (s, 3H, major), 3.22 (s, 2H, minor), 3.25 (s, 2H, major), 6.33 (s, 1H, minor), 6.42 (s, 1H, major), 6.73 (br s, 2H, major and minor), 6.79 (d, *J* = 4.5 Hz, 1H, minor), 6.86 (t, *J* = 4.5 Hz, 1H, major), 6.90 (d, *J* = 4.5 Hz, 1H major), 6.97 (t, *J* = 7.5 Hz, 1H, minor), 7.03 (d, *J* = 7.05 Hz, 1H, minor), 7.05–7.06 (m, 2H, major), 7.20 (d, *J* = 7.0 Hz, 1H, minor), 7.36 (d, *J* = 4.5 Hz, 1H, minor), 7.61 (d, *J* = 4.5 Hz, 1H, major) ppm; $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ = 16.7 ($CH_3$, major), 16.8 ($CH_3$, minor), 40.4 ($CH_2$, major), 43.1 ($CH_2$, minor), 113.6 (CH), 114.2 (CH), 118.3 (CH), 118.6 (CH), 120.1 (CH), 122.6 (CH), 122.7 (CH), 123.8 (CH), 124.4 (CH), 125.3, 127.0 (CH), 127.8 (CH), 129.9, 137.1, 137.6, 142.3, 144.9, 146.6, 147.8, 148.2, 149.7 ppm; IR (KBr): $\nu$(NH) 3124, $\nu(SO_2)$ 1246, 1143 $cm^{-1}$; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{15}H_{13}N_3O_2S_2Cl$: 366.0132, found: 366.0141.

**5.2.9.8. 6-Chloro-*N*-(1,1,3-trimethyl-1*H*-inden-5-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 51.** The above procedure was followed using inden-5-amine **40** (0.18 g, 1.05 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.27 g, 1.05 mmol) in dry pyridine (6.5 mL). Indenylsulfonamide **51** was obtained as a salmon foamy solid (0.15 g, 35%): mp 86–87 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.20 (s, 6H), 1.97 (s, 3H), 6.03 (d, *J* = 1.2 Hz, 1H), 6.87–6.90 (m, 2H), 6.95 (d, *J* = 1.5 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 4.5 Hz, 1H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 12.6 ($CH_3$), 24.4 ($CH_3$), 47.9, 114.0 (CH), 114.2 (CH), 118.3, 119.9 (CH), 120.2 (CH), 121.5 (CH), 133.3, 134.8, 137.7, 143.8 (CH), 145.5, 149.7, 152.6 ppm; IR (KBr): $\nu$(NH) 3117, $\nu(SO_2)$ 1250, 1142 $cm^{-1}$; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}N_3O_2S_2Cl$: 394.0445, found: 394.0453.

**5.2.9.9. 6-Chloro-*N*-(6-methoxy-2,3-dimethyl-1*H*-inden-5-yl)-imdazo[2,1-*b*][1,3]thiazole-5-sulfonamide 52.** The above procedure was followed using inden-5-amine **46** (64.0 mg, 0.34 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (87.0 mg, 0.34 mmol) in dry pyridine (2.0 mL). Indenylsulfonamide **52** was obtained as an off-white foamy solid (40.0 mg, 29%): mp 163–164 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.95 (s, 3H), 2.00 (s, 3H), 3.14 (s, 2H), 3.62 (s, 3H), 6.79 (s, 1H), 6.90 (d, *J* = 4.5 Hz, 1H), 7.72 (d, *J* = 4.5 Hz, 1H) ppm; $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ = 10.2 ($CH_3$), 13.8 ($CH_3$), 42.4 ($CH_2$), 55.8 ($CH_3$), 106.7 (CH), 112.6 (CH), 113.7 (CH), 118.2, 120.1 (CH), 122.2, 131.7, 136.9, 138.6, 140.7, 141.1, 147.9, 149.4 ppm; IR (KBr): $\nu$(NH) 3114, $\nu(SO_2)$ 1253, 1146 $cm^{-1}$; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}N_3O_3S_2Cl$: 410.0394, found: 410.0397.

### 5.3. 5-HT$_6$ binding assay

Membranes from HEK-293 with human 5-HT$_6$ receptor expressed were supplied by Receptor Biology Inc. (Beltsville, MD, USA). In these membranes the receptor concentration is 2.18 pmol/mg protein and the protein concentration is 9.17 mg/mL. The binding assays were performed as described by Roth et al.[21] with slight modifications. The commercial membrane is diluted (dilution 1:40) with the binding buffer: 50 mM Tris–HCl, 10 mM $MgCl_2$ and 0.5 mM EDTA at pH 7.4. The radioligand used was [$^3$H]-LSD at 2.7 nM, and the final volume was 200 μL. The incubation was initiated by addition of 100 μL of membrane (22.9 μg of protein), and the incubation time was 60 min at 37 °C. After incubation, the membranes were collected onto polyethylenimine-pretreated glass fiber filters (Schleicher & Schnell 3362). The filters were washed with buffer (50 mM Tris Cl, pH 7.4). Then, filter sections were transferred to vials, and liquid scintillation cocktail was added to each vial. Nonspecific binding was determined with 100 μM serotonin. Stock compound solutions were prepared in DMSO and diluted with phosphate buffer solution (PBS) not exceeding 2% of DMSO at final concentration. Competition binding data were analyzed by using the LIGAND program,[22] and assays were performed in triplicate determinations for each point. A linear regression line of data points is plotted, from which the concentration of competing ligand which displaces 50% of the specific binding of the radioligand ($IC_{50}$ value) is determined and the $K_i$ value is determined based upon the Cheng–Prusof equation: $K_i = IC_{50}/(1 + L/K_D)$ were L is the concentration of free radioligand used in the assay and $K_D$ is the dissociation constant of the radioligand for the receptor.

### 5.4. Adenylyl cyclase activity assay

Functional effects of the compounds were evaluated by cAMP measurements on HEK-293F cells stably expressing the human 5-HT$_6$ receptor using a Homogeneous Time Resolved Fluorescence (HTRF) assay format. Cell culture media and reagents were pur-

chased from Gibco (Paislay, UK). HTRF cAMP kit was purchased from CisBio (Bagnols, France). After overnight serum-free medium incubation, cell suspension (20,000 cells per well) was added in 96-well culture plate in incubation buffer composed of Ham's F12 medium plus 1 mM 3-isobutyl-1-methyl-xanthine (IBMX) and 20 μM pargyline. Stock compound solutions were prepared in DMSO and diluted with phosphate buffer solution (PBS) not exceeding 2% of DMSO at final concentration. Forty microliters of cell suspension and 10 μL of either compound or vehicle (DMSO) were added to each well at indicated concentrations for 30 min at 37 °C, in either absence or presence (in antagonist experiments) of 5-HT. The reaction was stopped with 25 μL of cryptate and 25 μL of cross-linked allophycocyanin (XL-665). Plates were incubated for 1 h at room temperature and read at 665 nm/620 nm using a RubyStar Plate reader (BMG LabTech).[9,23,24]

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.08.006.

## References and notes

1. Alcalde, E.; Mesquida, N.; López-Pérez, S.; Frigola, J.; Mercè, R. *J. Med. Chem.* **2009**, *52*, 675.
2. Glennon, R. A. *J. Med. Chem.* **2003**, *46*, 2795.
3. (a) Liu, K. G.; Robichaud, A. J. *Drug Dev. Res.* **2009**, *70*, 145; (b) Johnson, C. N.; Ahmed, M.; Miller, N. D. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 642; (c) Geldenhuys, W. J.; Van der Schyf, C. J. *Curr. Top. Med. Chem.* **2008**, *8*, 1035.
4. (a) Heal, D. J.; Smith, S. L.; Fisas, A.; Codony, X.; Buschmann, H. *Pharmacol. Ther.* **2008**, *117*, 207; (b) Nichols, D. E. *Chem. Rev.* **2008**, *108*, 1614.
5. Glennon, R. A.; Lee, M.; Rangisetty, J. B.; Dukat, M.; Roth, B. L.; Savage, J. E.; McBride, A.; Rauser, L.; Hufesien, S.; Lee, D. K. H. *J. Med. Chem.* **2000**, *43*, 1011.
6. Tsai, Y.; Dukat, M.; Slassi, A.; MacLean, N.; Demchyshyn, L.; Savage, J. E.; Roth, B. L.; Hufesein, S.; Lee, M.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2295.
7. Mercè, R.; Andaluz, B.; Frigola, J. World Patent WO 2003042175 A1, 2003; *Chem. Abstr.* **2003**, *138*, 401602.
8. Holenz, J.; Mercè, R.; Díaz, J. L.; Guitart, X.; Codony, X.; Dordal, A.; Romero, G.; Torrens, A.; Mas, J.; Andaluz, B.; Hernández, S.; Monroy, X.; Sánchez, E.; Hernández, E.; Pérez, R.; Cubí, R.; Sanfeliu, O.; Buschmann, H. *J. Med. Chem.* **2005**, *48*, 1781.
9. Fisas, A.; Codony, X.; Romero, G.; Dordal, A.; Giraldo, J.; Mercè, R.; Holenz, J.; Heal, D.; Buschmann, H.; Pauwels, P. J. *Br. J. Pharmacol.* **2006**, *148*, 973.
10. Cole, D. C.; Stock, J. R.; Lennox, W. J.; Bernotas, R. C.; Ellingboe, J. W.; Boikess, S.; Coupet, J.; Smith, D. L.; Leung, L.; Zhang, G.-M.; Feng, X.; Kelly, M. F.; Galante, R.; Huang, P.; Dawson, L. A.; Marquis, K.; Rosenzweig-Lipson, S.; Beyer, C. E.; Schechter, L. E. *J. Med. Chem.* **2007**, *50*, 5535.
11. Schechter, L. E.; Lin, Q.; Smith, D. L.; Zhang, G.; Shan, Q.; Platt, B.; Brandt, M. R.; Dawson, L. A.; Cole, D.; Bernotas, R.; Robichaud, A.; Rosenzweig-Lipson, S.; Beyer, C. E. *Neuropsychopharmacology* **2007**, 1.
12. Abate, C.; Kolanos, R.; Dukat, M.; Setola, V.; Roth, B. L.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3510.
13. Cole, D. C.; Lennox, W. J.; Stock, J. R.; Ellingboe, J. W.; Mazandarani, H.; Smith, D. L.; Zhang, G.; Tawa, G. J.; Schechter, L. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4780. and references cited therein.
14. Cole, D. C.; Lennox, W. J.; Lombardi, S.; Elligboe, J. W.; Bernotas, R. C.; Tawa, G. J.; Mazandarani, H.; Smith, D. L.; Zhang, G.; Coupet, J.; Schechter, L. E. *J. Med. Chem.* **2005**, *48*, 353.
15. Schechter, L. E.; Ring, R. H.; Beyer, C. E.; Hughes, Z. A.; Khawaja, X.; Malberg, J. E.; Rosenzwieg-Lipson, S. *J. Am. Soc. Exp. NeuroTher.* **2005**, *2*, 590.
16. Pullagurla, M. R.; Dukat, M.; Setola, V.; Roth, B.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3355.
17. (a) Siripurapu, U.; Kolanos, R.; Dukat, M.; Roth, B. L.; Glennon, R. A. *Bioorg. Med. Chem Lett.* **2006**, *16*, 3793; (b) Sikazwe, D.; Bondarev, M. L.; Dukat, M.; Rangisetty, J. B.; Roth, B. L.; Glennon, R. A. *J. Med. Chem.* **2006**, *49*, 5217.
18. Dukat, M.; Philip, D.; Mosier, P. D.; Kolanos, R.; Roth, B. L.; Glennon, R. A. *J. Med. Chem.* **2008**, *51*, 603. and references cited therein.
19. Alcalde, E.; Mesquida, N.; Frigola, J.; López-Pérez, S.; Mercè, R. *Org. Biomol. Chem.* **2008**, *6*, 3795. and references cited therein.
20. Frigola, J.; Mercè, R.; Holenz, J.; Alcalde, E.; Mesquida, N.; López-Pérez, S. World Patent WO 2007054257 A2, 2007; *Chem. Abstr.* **2007**, *146*, 521555.
21. Roth, B. L.; Craigo, S. C.; Choudhary, M. S.; Uluer, A.; Monsma, F. J., Jr.; Shen, Y.; Meltzer, H. Y.; Sibley, D. R. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 1403.
22. Munson, P. J.; Rodbard, D. *Anal. Biochem.* **1980**, *107*, 220.
23. Romero, G.; Sánchez, E.; Pujol, M.; Pérez, P.; Codony, X.; Holenz, J.; Buschmann, H.; Pauwels, P. J. *Br. J. Pharmacol.* **2006**, *148*, 1133.
24. Romero, G.; Pujol, M.; Pérez, P.; Buschmann, H.; Pauwels, P. J. *J. Pharmacol. Toxicol. Methods* **2007**, *55*, 144.

# Supplementary Data

## Indene-Based Frameworks Targeting the 5-$HT_6$ Serotonin Receptor: Ring Constraint in Indenylsulfonamides Using Cyclic Amines and Structurally Abbreviated Counterparts.**

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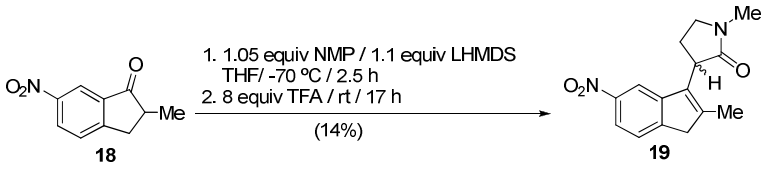
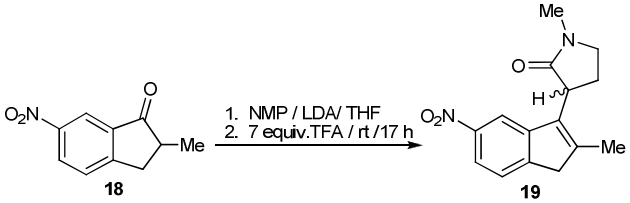
## ASSAYS RELATED WITH THE PREPARATION OF COMPOUND 19




| Assay[a,b] | NMP (equiv) | LDA (equiv) | T (ºC) | Time (h) | Rt[c] (%) |
|---|---|---|---|---|---|
| 1 | 1.05 | 1.1 | − 78 | 2.5 | 17% |
| 2 | 1.05 | 2.1 | − 78 | 2.5 | 14% |
| 3 | 1.25 | 1.5 | − 78<br>rt | 2.5<br>2 | 10% |

[a] Reactions 1 equiv. respectively to 2-methyl-6-nitro-2,3-dihydro-1*H*-inden-1-one **18**.

[b] Reaction conditions reported by Heathcock et al.:

(a) *J. Org. Chem.* **1985**, *50*, 3019-3022. (b) *J. Org. Chem.* **1990**, *55*, 132-157.

[c] Yield isolated after purification by chromatography.

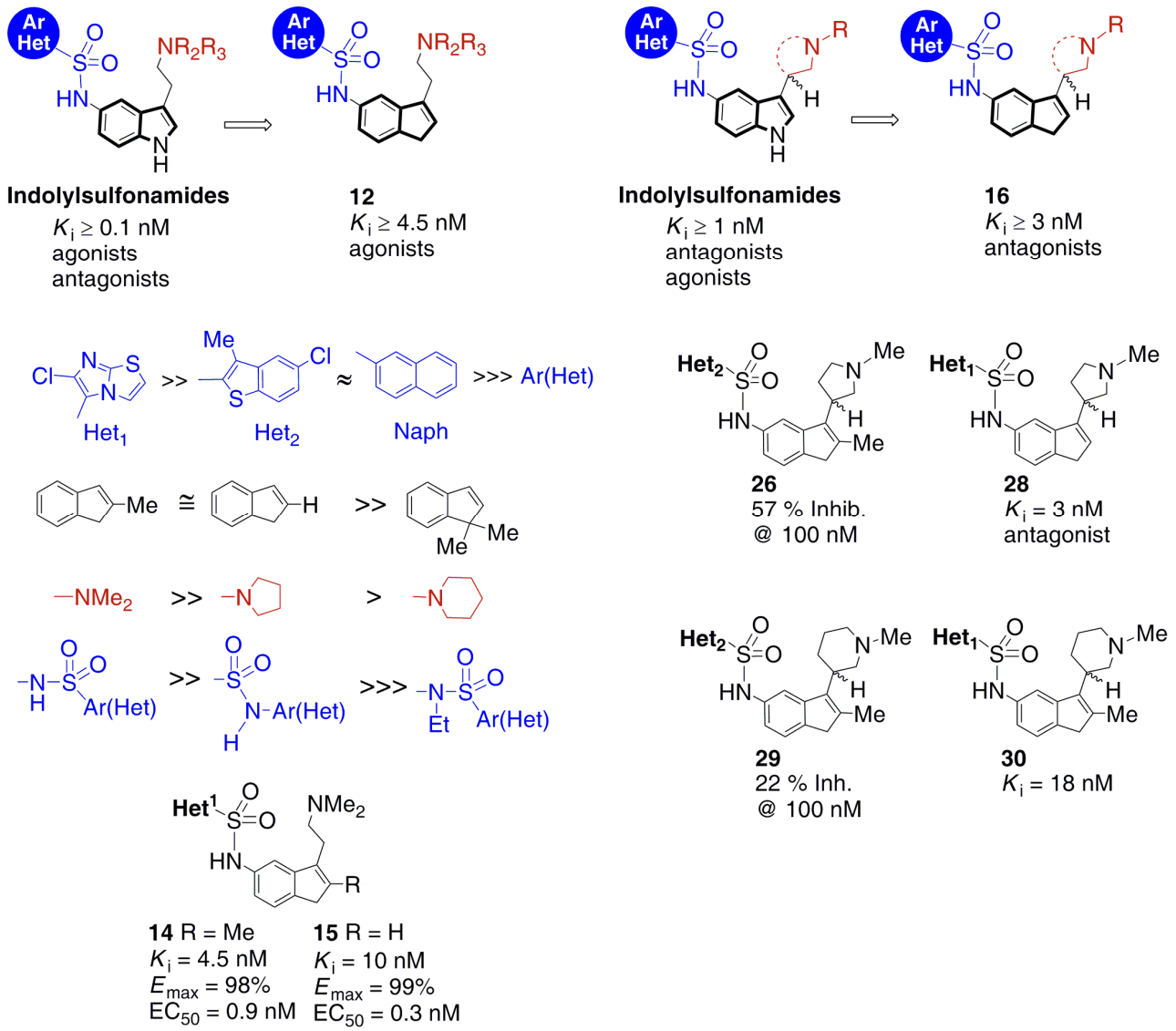
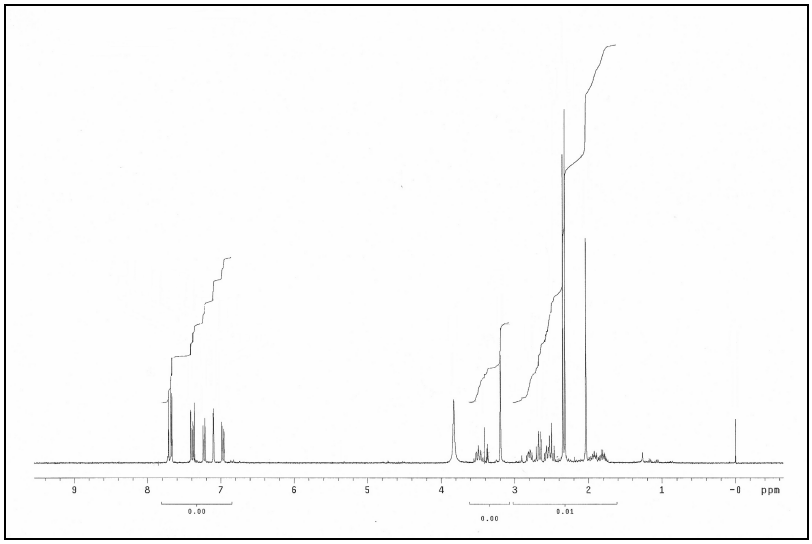



**Figure S1.** Further studies on the indole-to-indene core change within 5-$HT_6$ serotonin receptor ligands

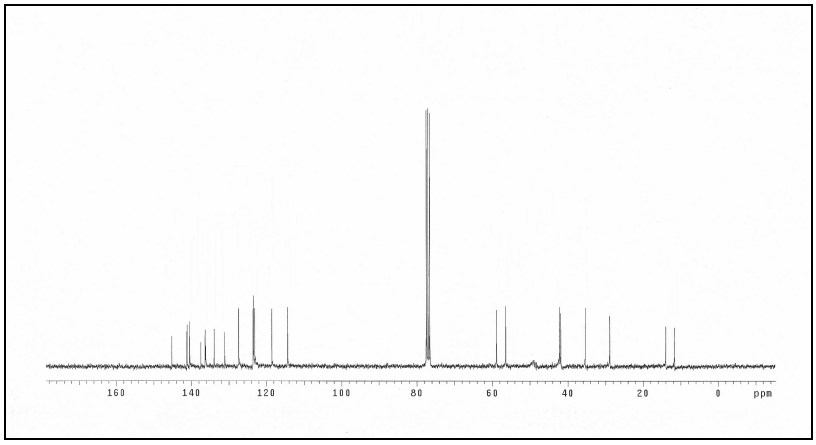
**NMR SPECTRA AND ESI (+)-HRMS SPECTRA OF TARGETED COMPOUNDS**

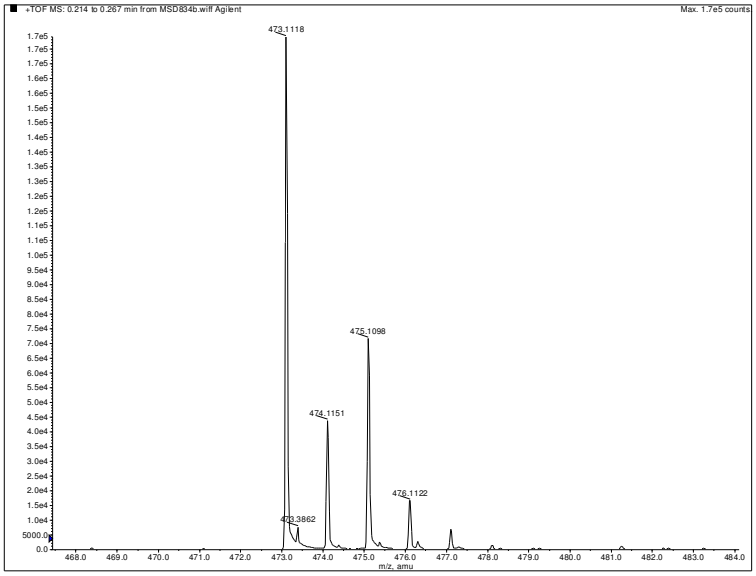
- **5-Chloro-3-methyl-*N*-[2-methyl-3-(1-methylpyrrolidin-3-yl)-1*H*-inden-5-yl]benzo[*b*]thiophene- 2-sulfonamide 26**

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



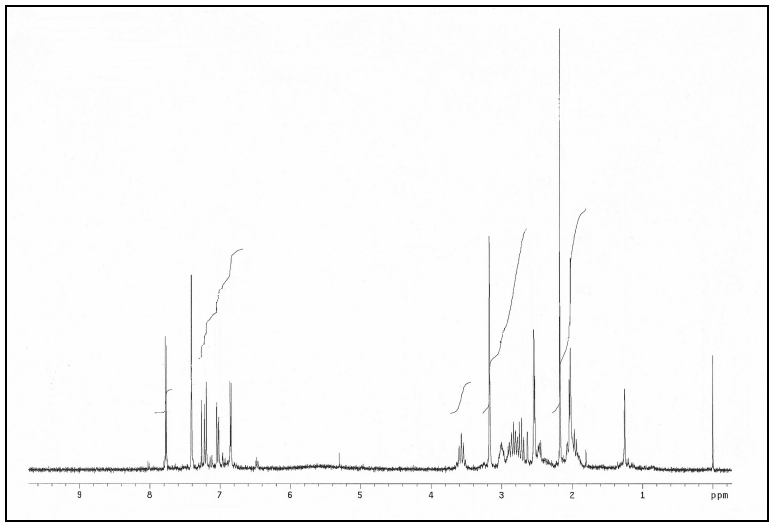

$^{13}$C NMR (75.4 MHz, $CDCl_3$)



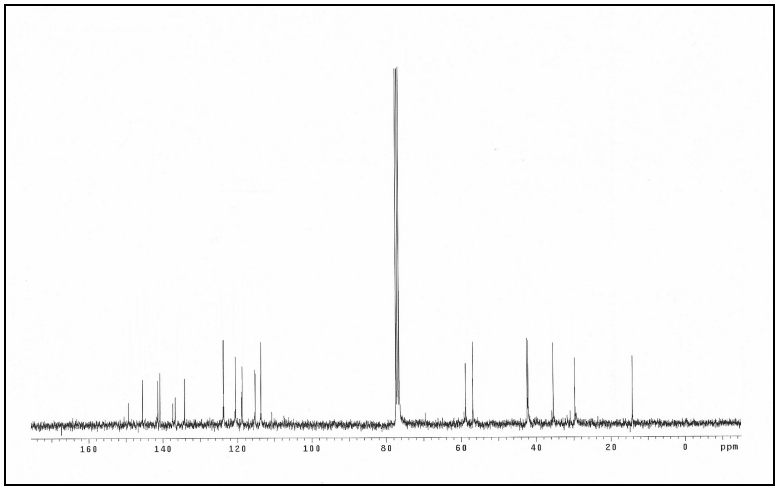



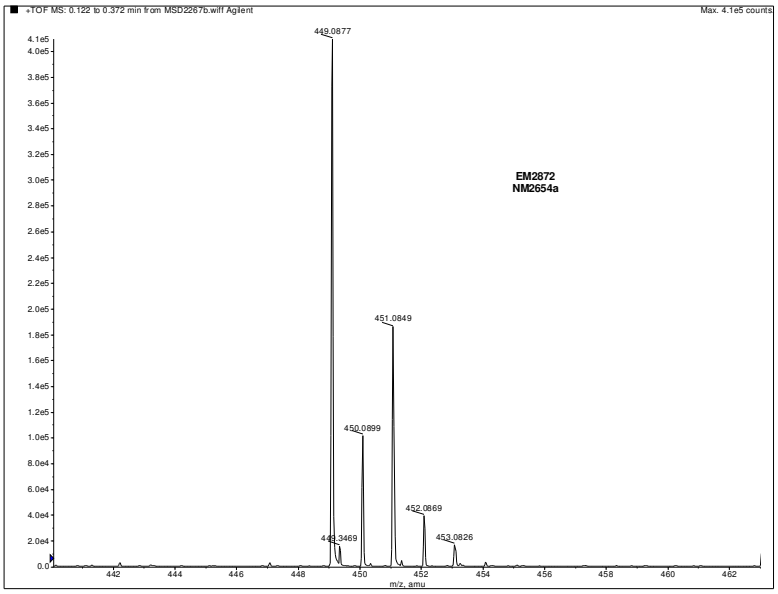
- **6-Chloro-*N*-[2-methyl-3-(1-methylpyrrolidin-3-yl)-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 27**

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

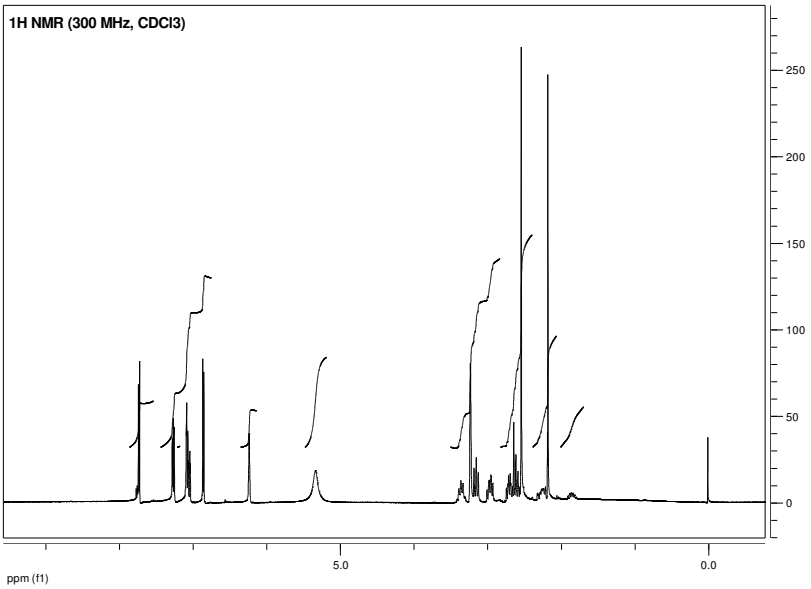


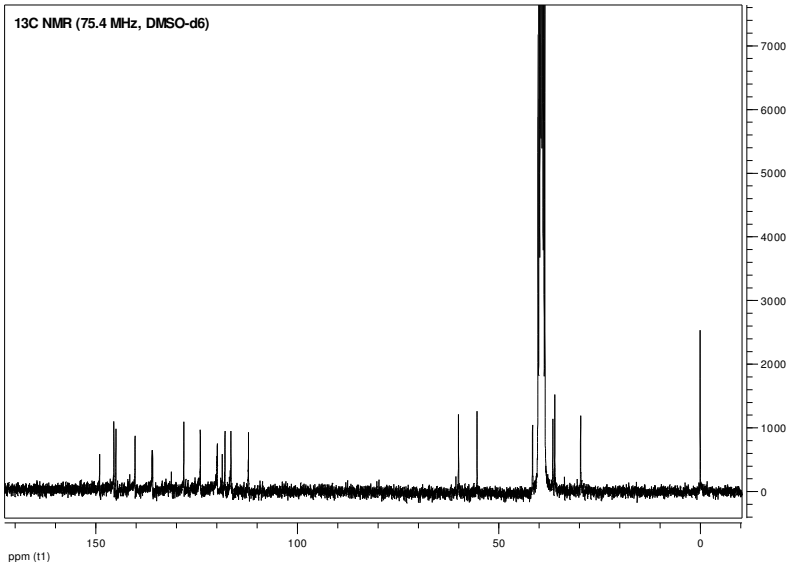

$^{13}$C NMR (75.4 MHz, $CDCl_3$)

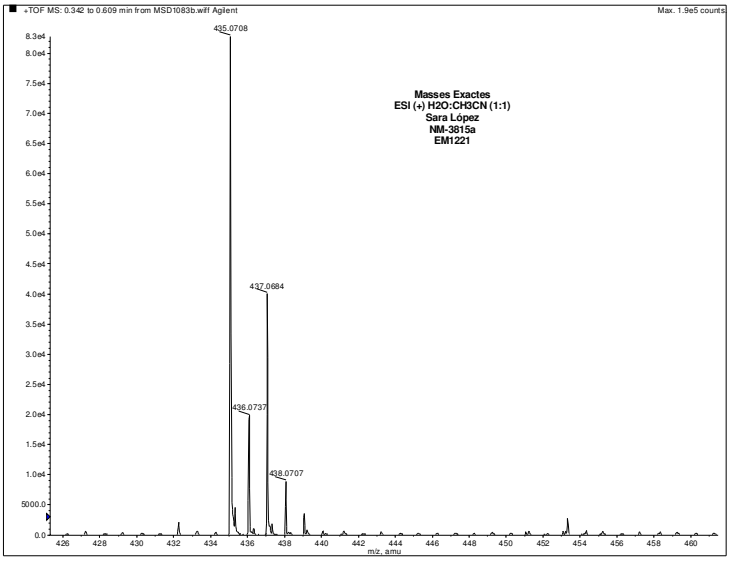


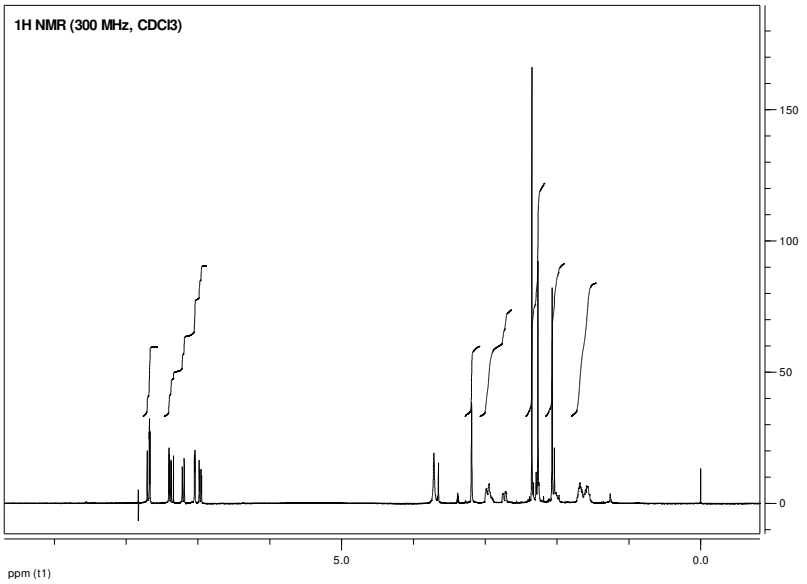
- **6-Chloro-*N*-[3-(1-methylpyrrolidin-3-yl)-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 28**

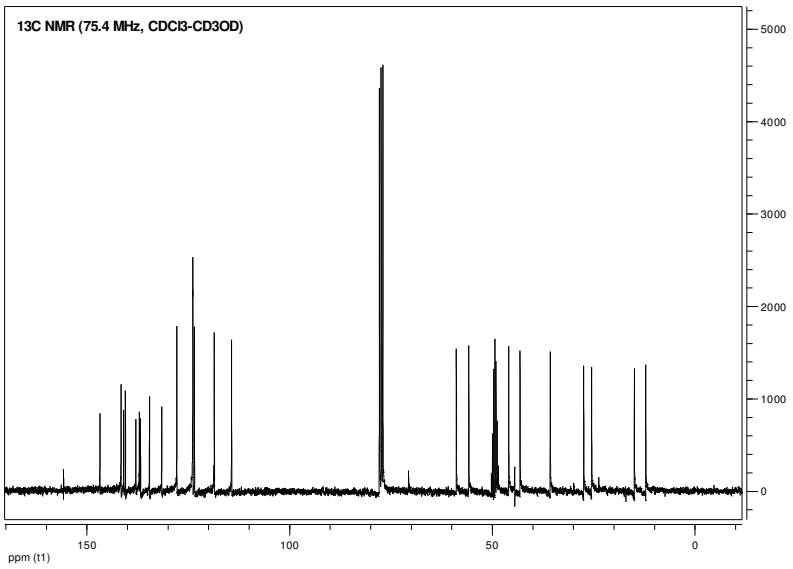


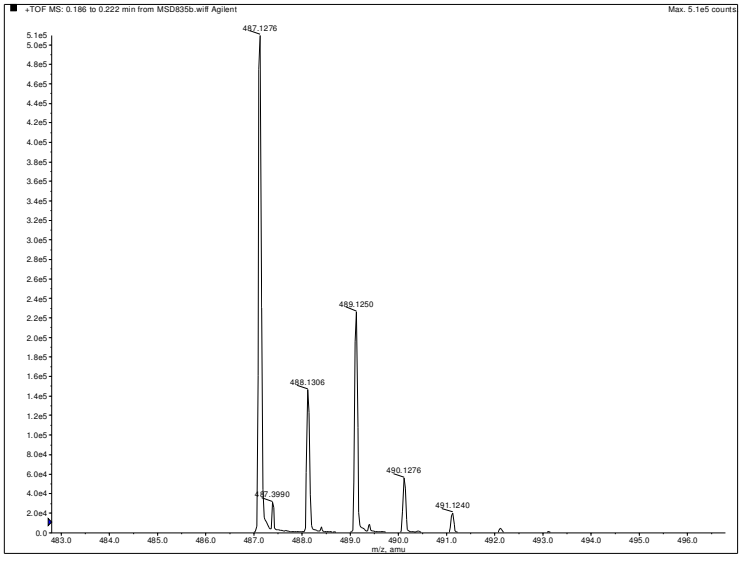



- **5-Chloro-3-methyl-*N*-[2-methyl-3-(1-methylpiperidin-3-yl)-1*H*-inden-5-yl]benzo[*b*]thiophene- 2-sulfonamide 29**

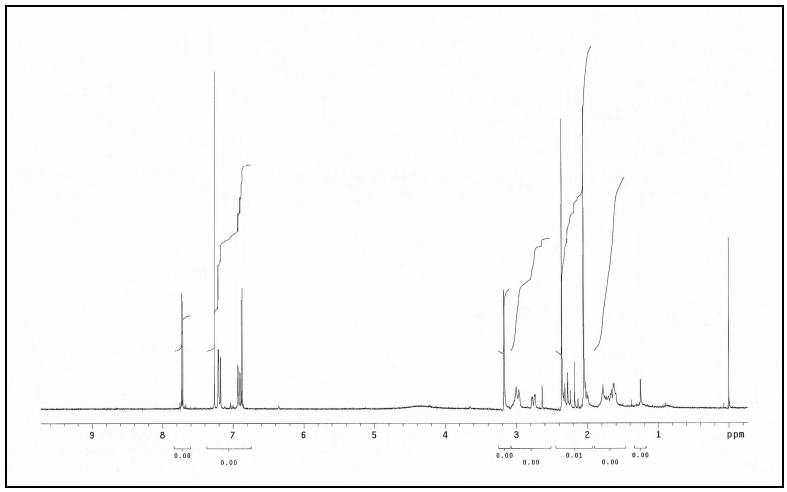


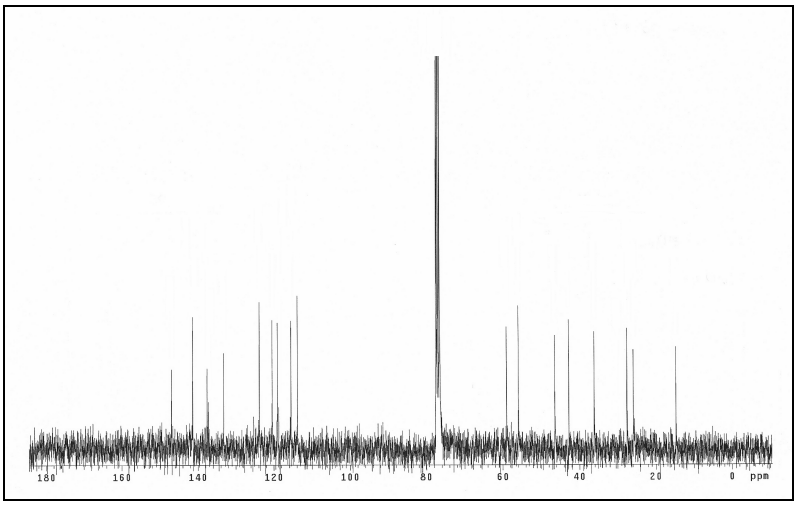



- **6-Chloro-*N*-[2-methyl-3-(1-methylpiperidin-3-yl)-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 30**

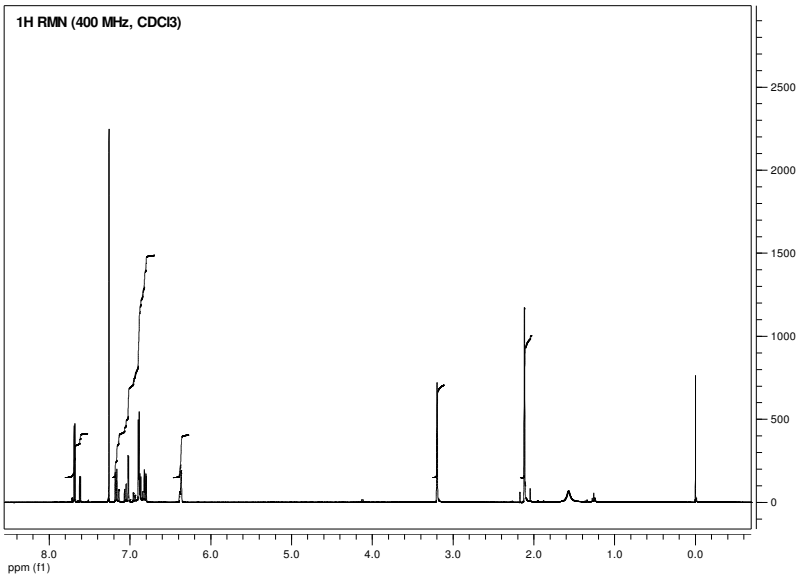
$^{1}$H NMR (300 MHz, $CDCl_3$)

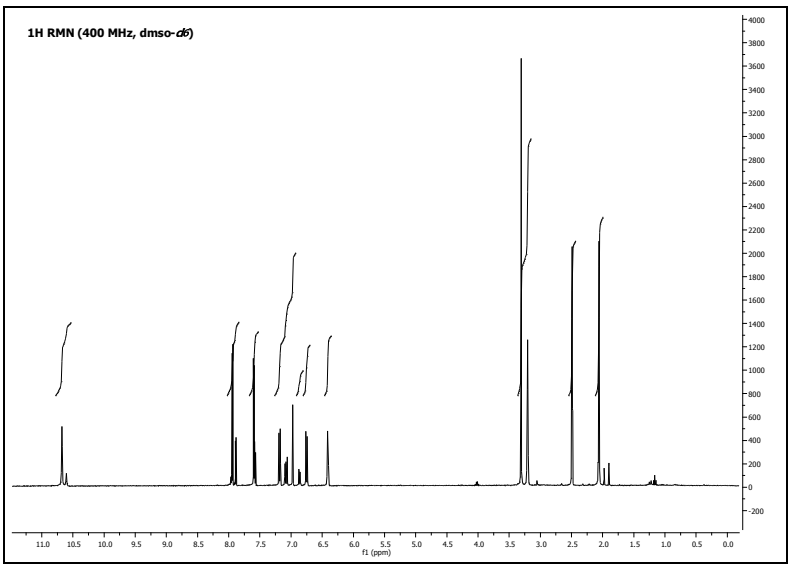


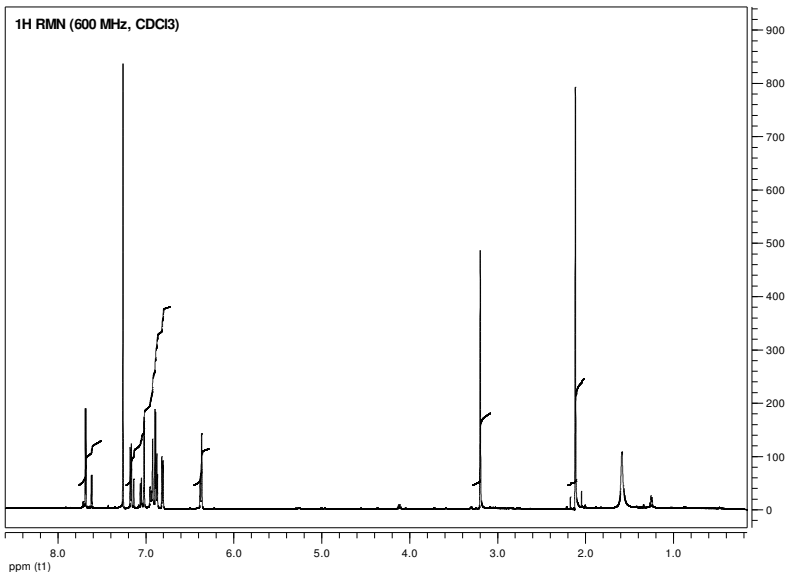

$^{13}$C NMR (75.4 MHz, $CDCl_3$)



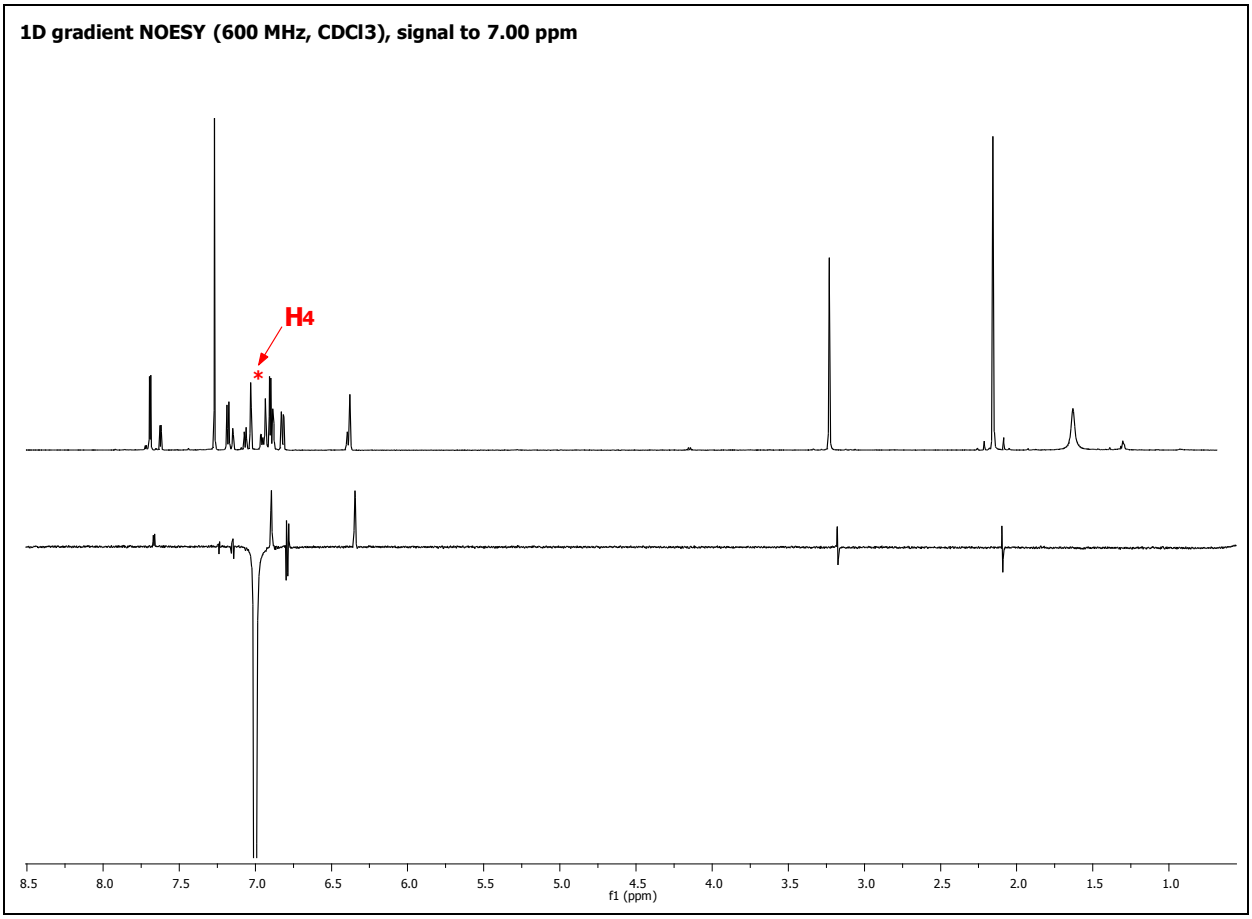
- **6-Chloro-*N*-(2-methyl-1*H*-inden-5-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 47 and 6-chloro-*N*-(2-methyl-1*H*-inden-6-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 48**

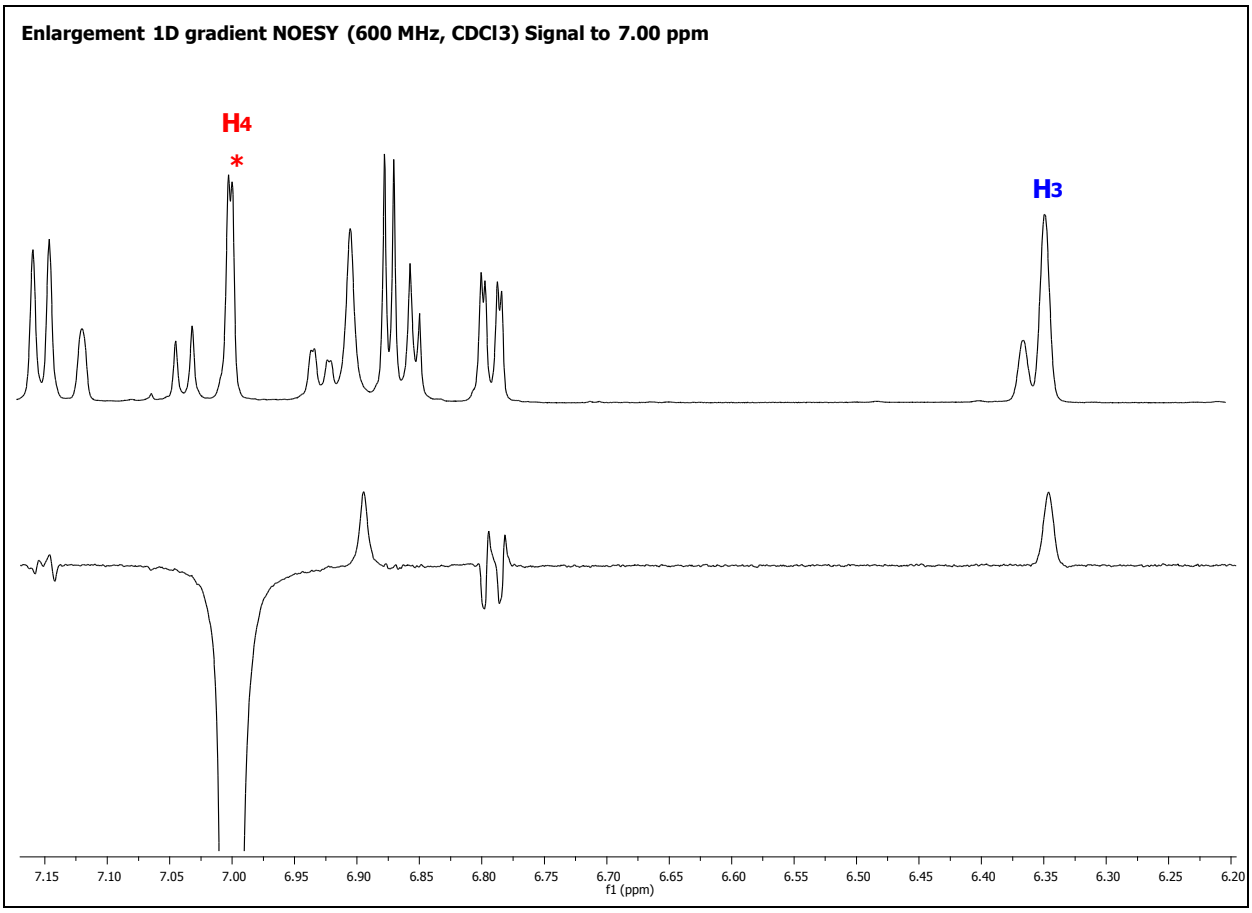


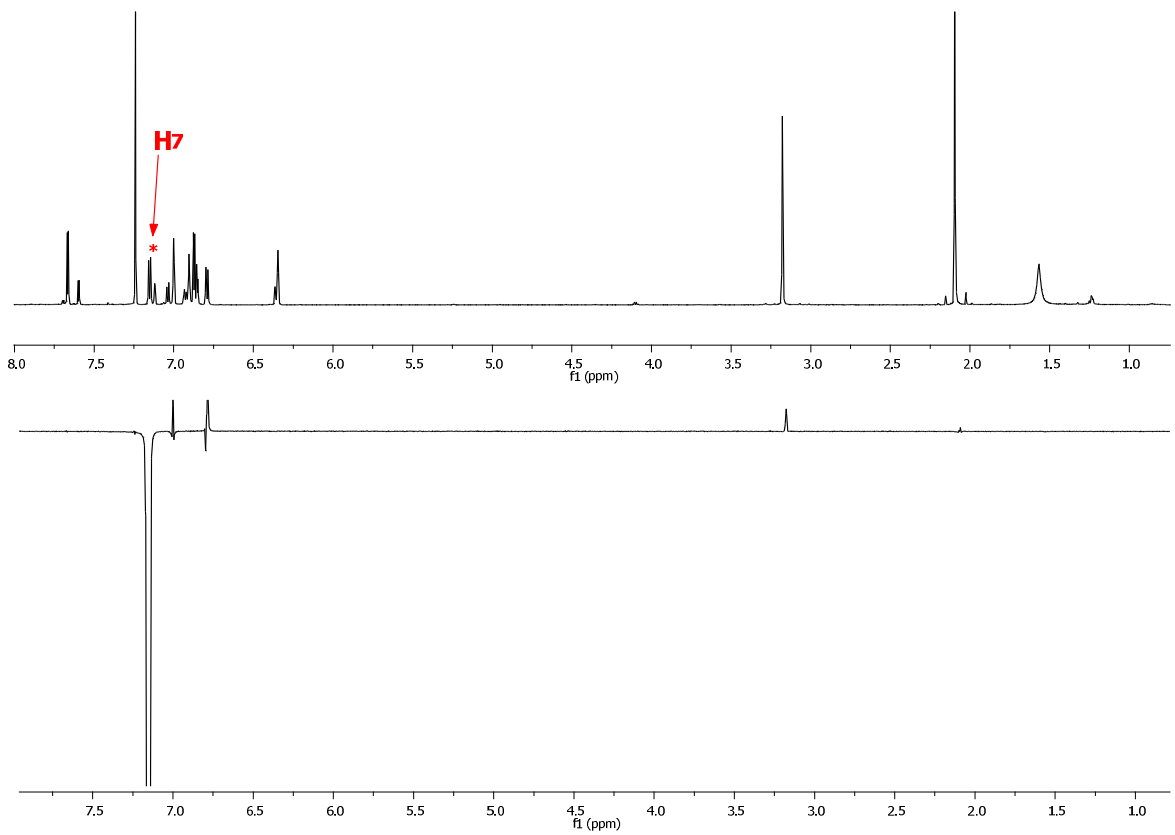



➢ **Compound 47 (major isomer)**

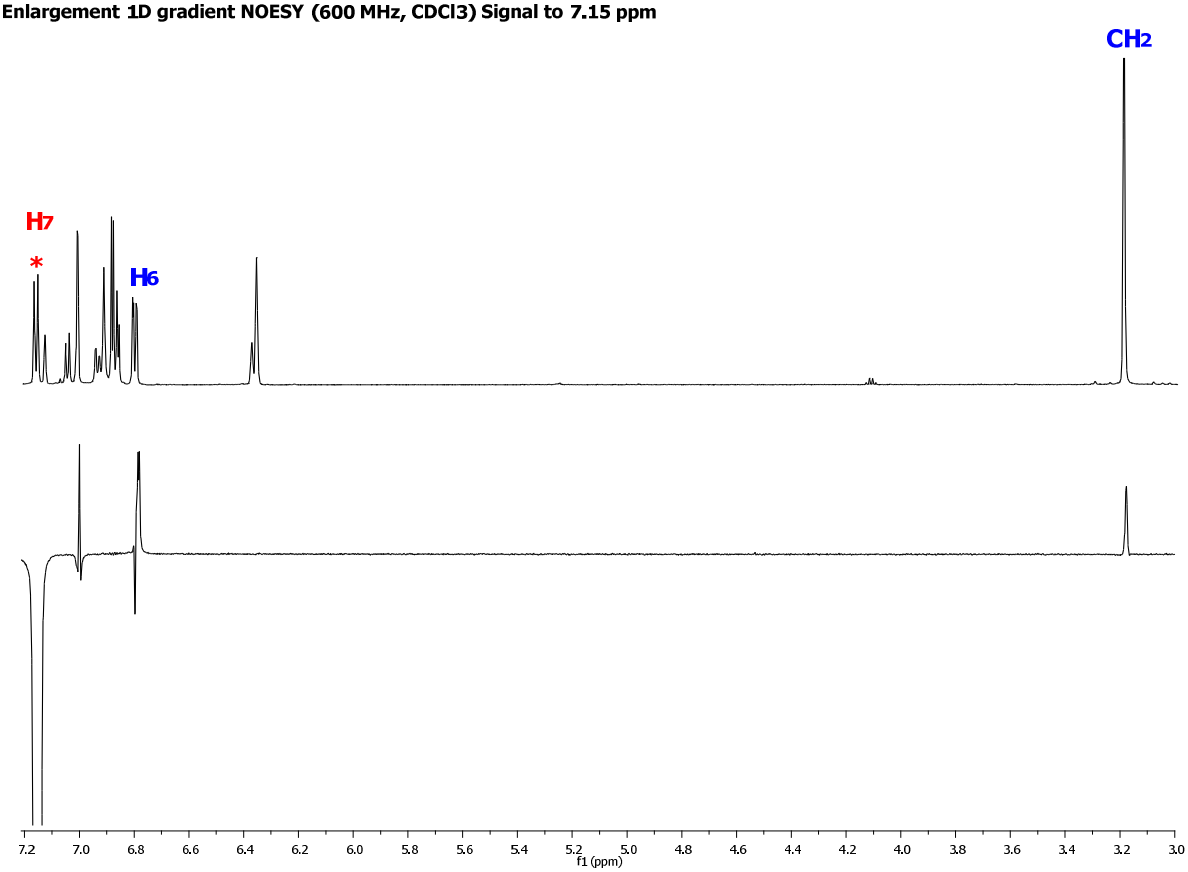


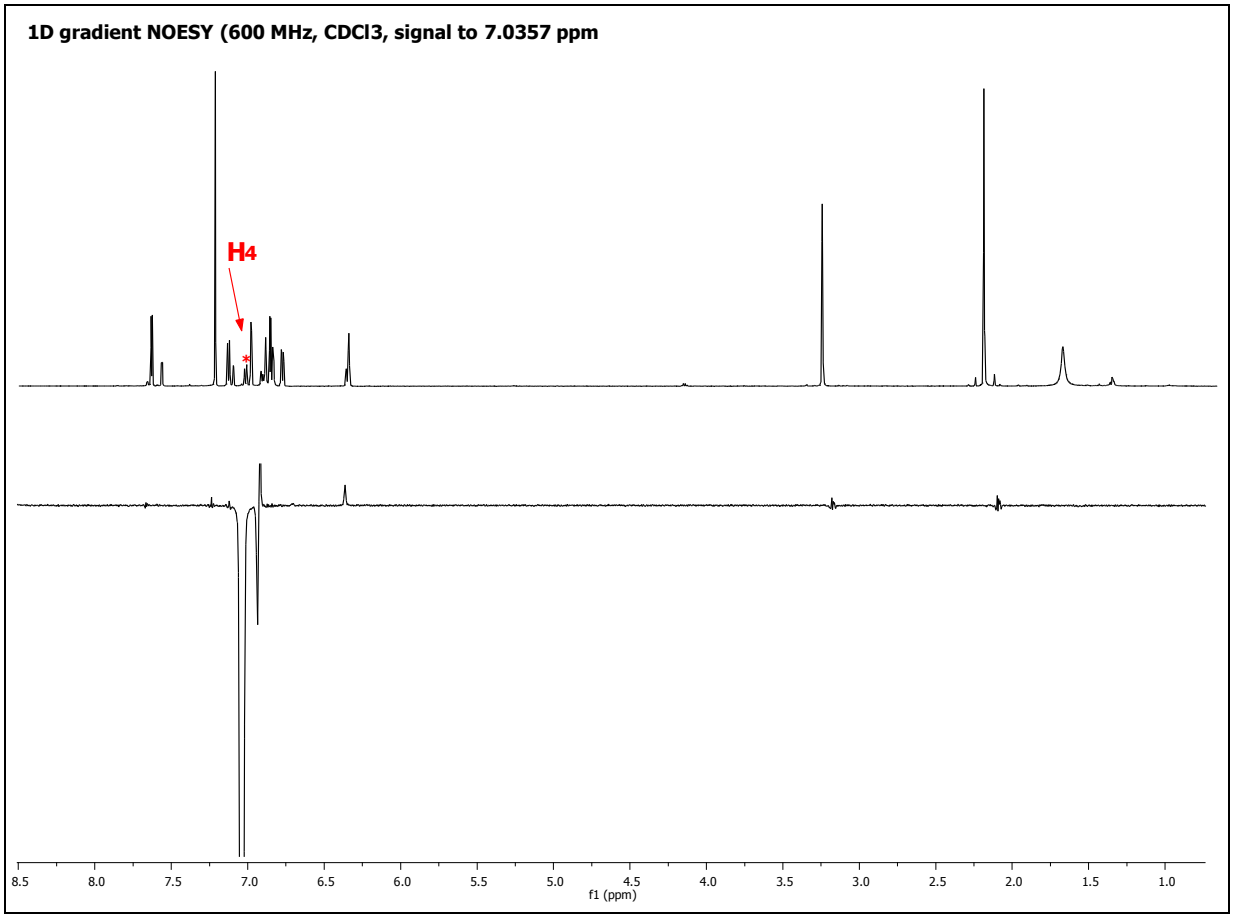
**1D gradient NOESY (600 MHz, CDCl3), signal to 7.15 ppm**

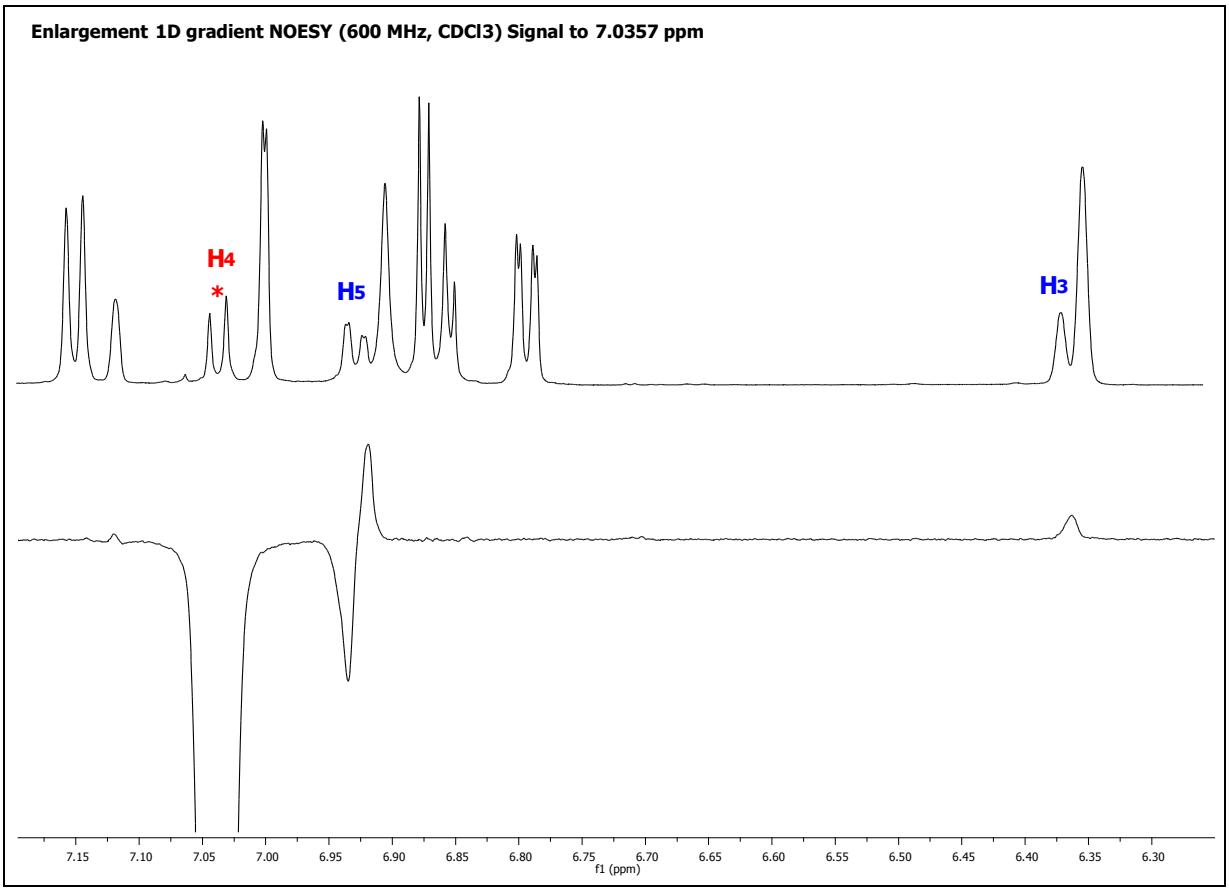



**Enlargement 1D gradient NOESY (600 MHz, CDCl3) Signal to 7.15 ppm**

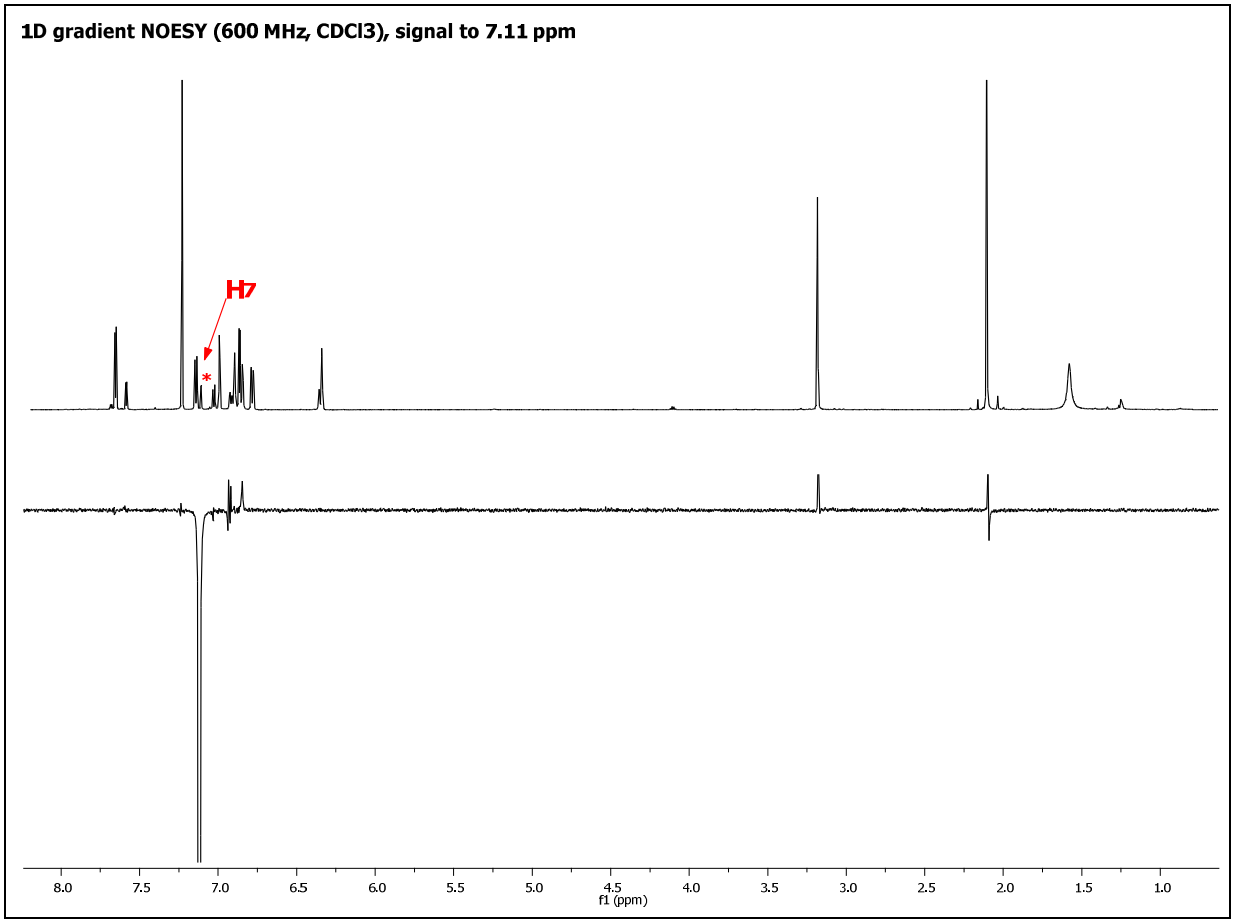


➢ **Compound 48 (minor isomer)**

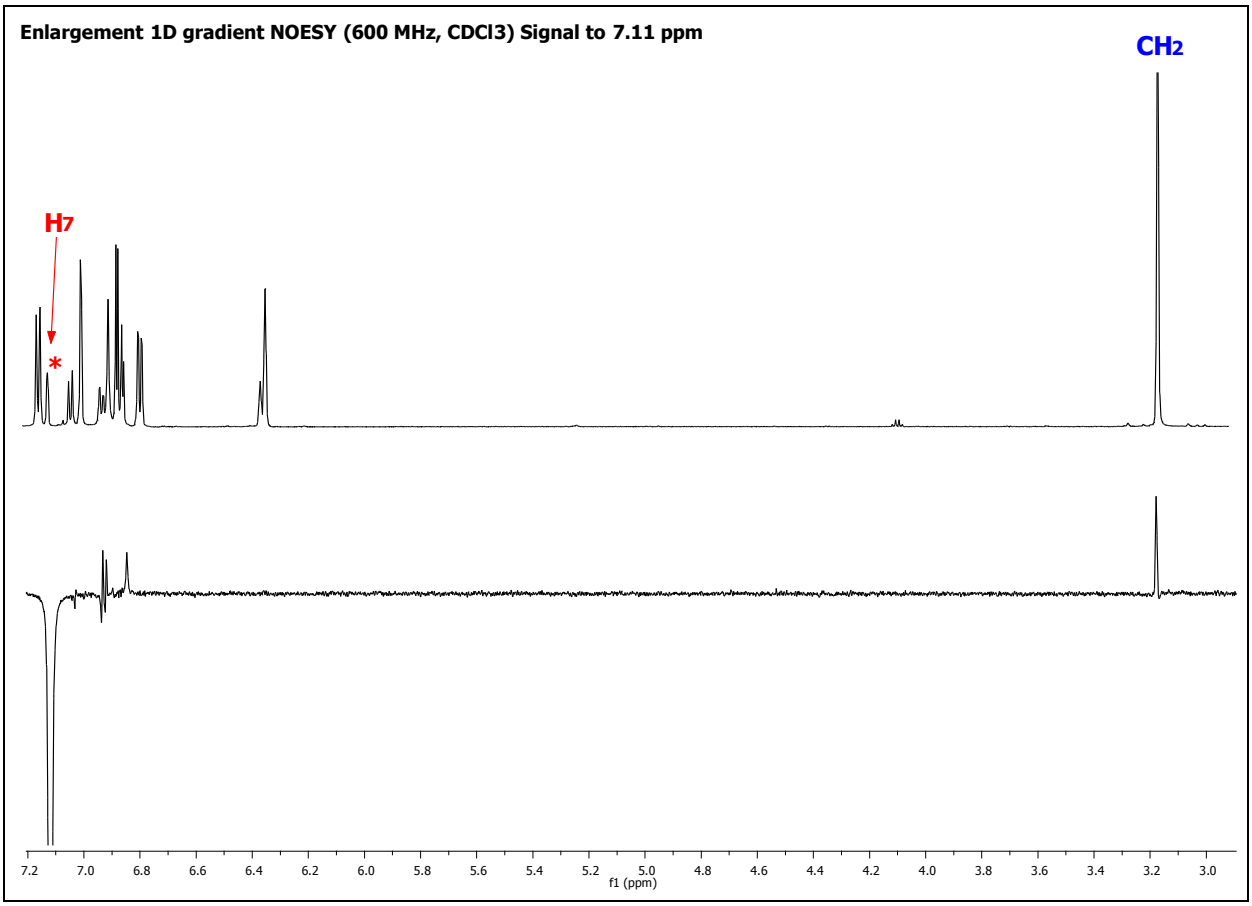


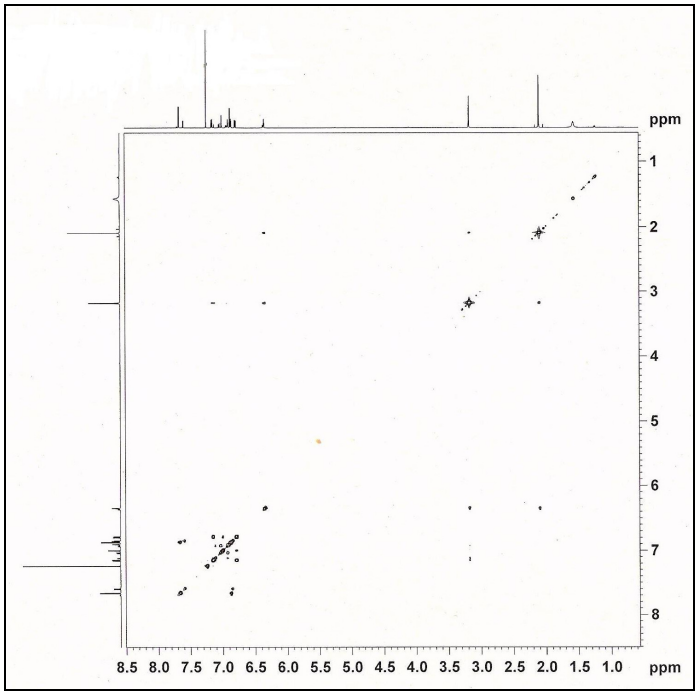
**1D gradient NOESY (600 MHz, CDCl3), signal to 7.11 ppm**

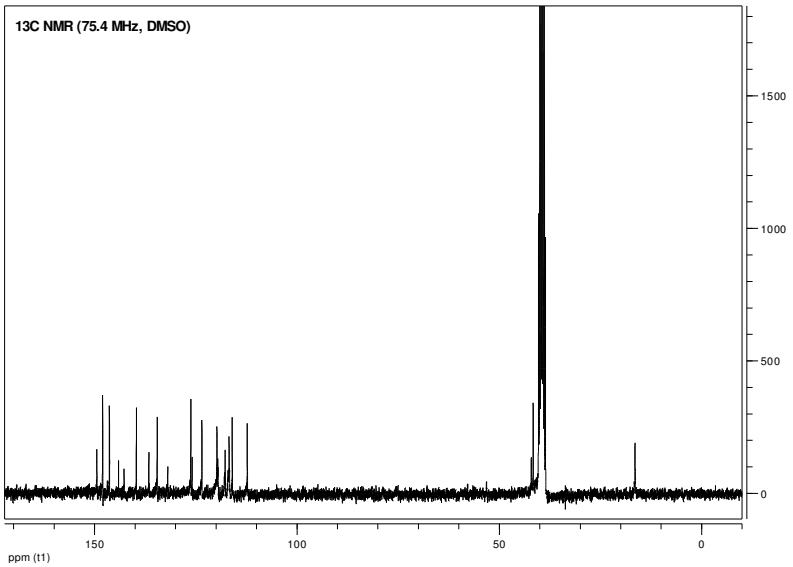


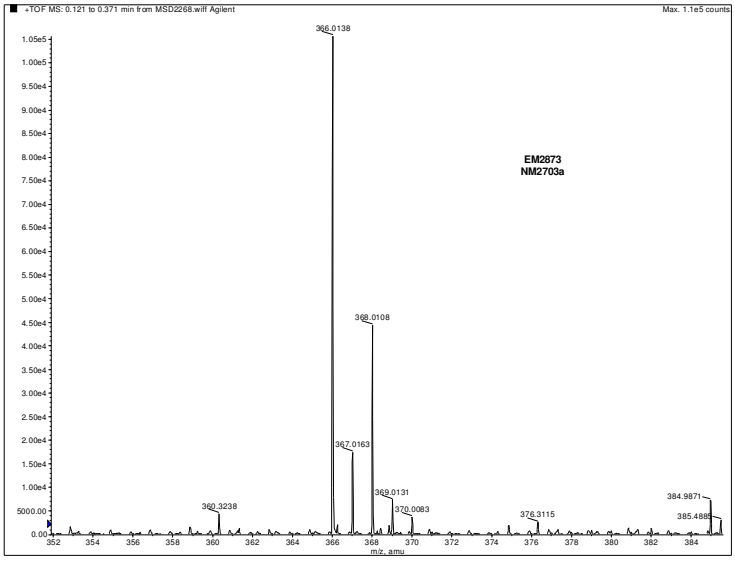

**Enlargement 1D gradient NOESY (600 MHz, CDCl3) Signal to 7.11 ppm**



2D gCOSY (600 MHz, $CDCl_3$)

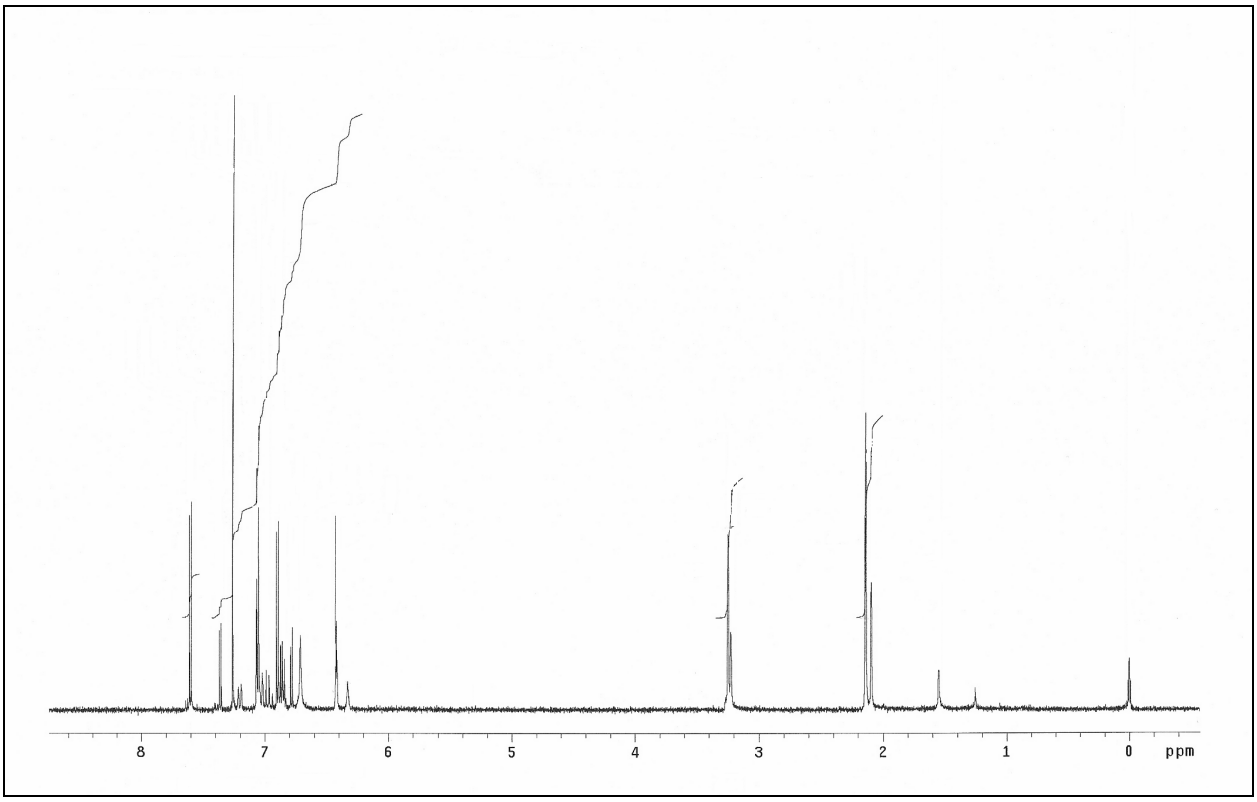


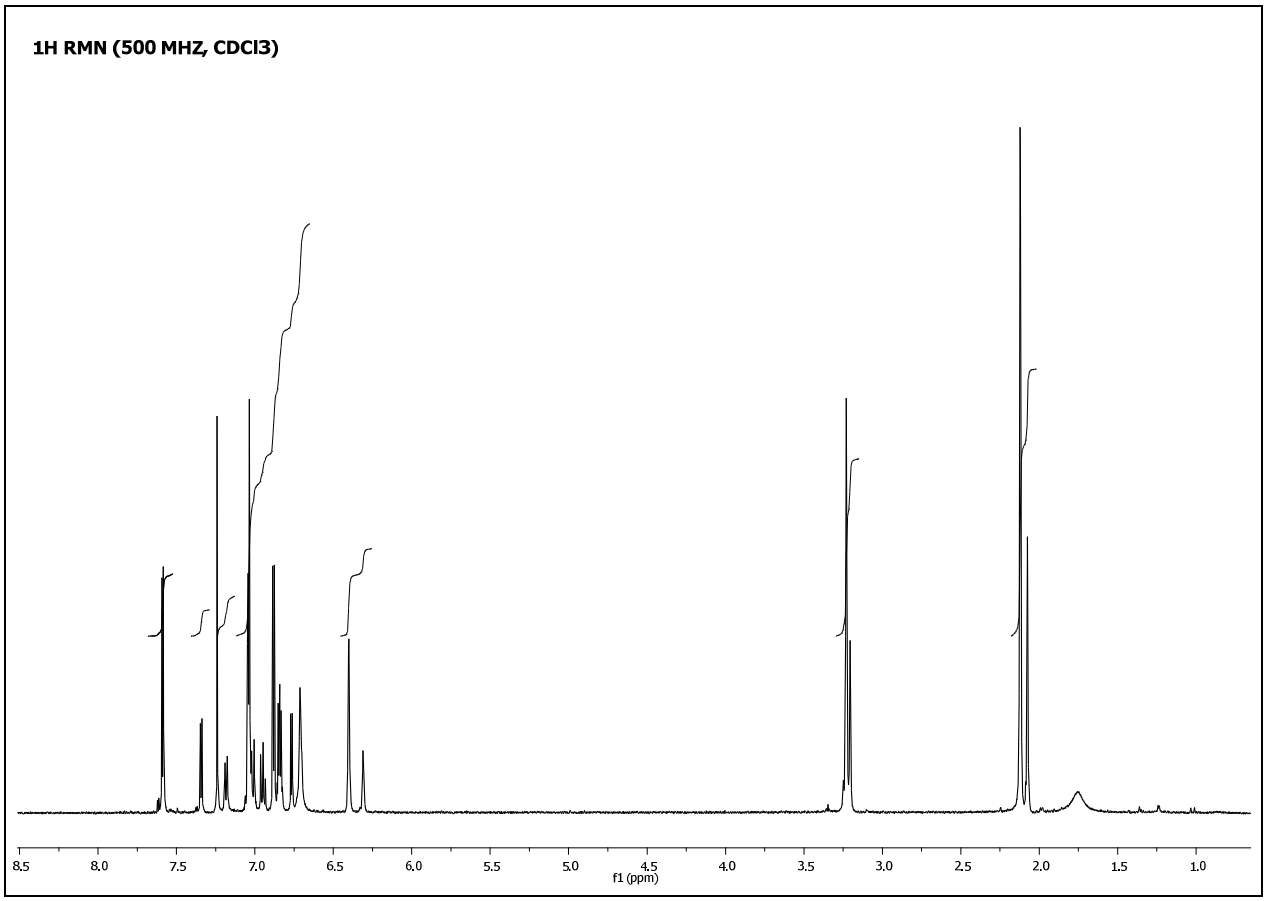



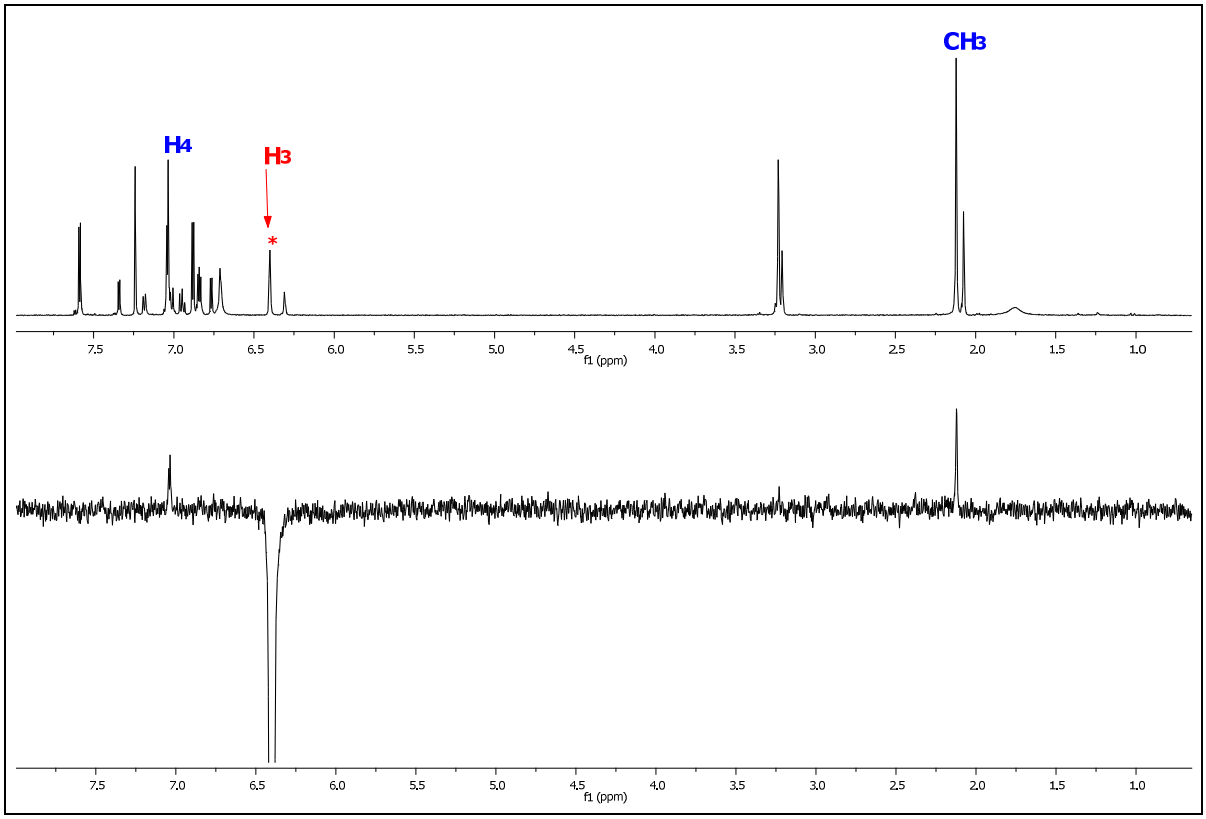
- **6-Chloro-*N*-(2-methyl-1*H*-inden-7-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 49 and 6-chloro-*N*-(2-methyl-1*H*-inden-4-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 50**

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

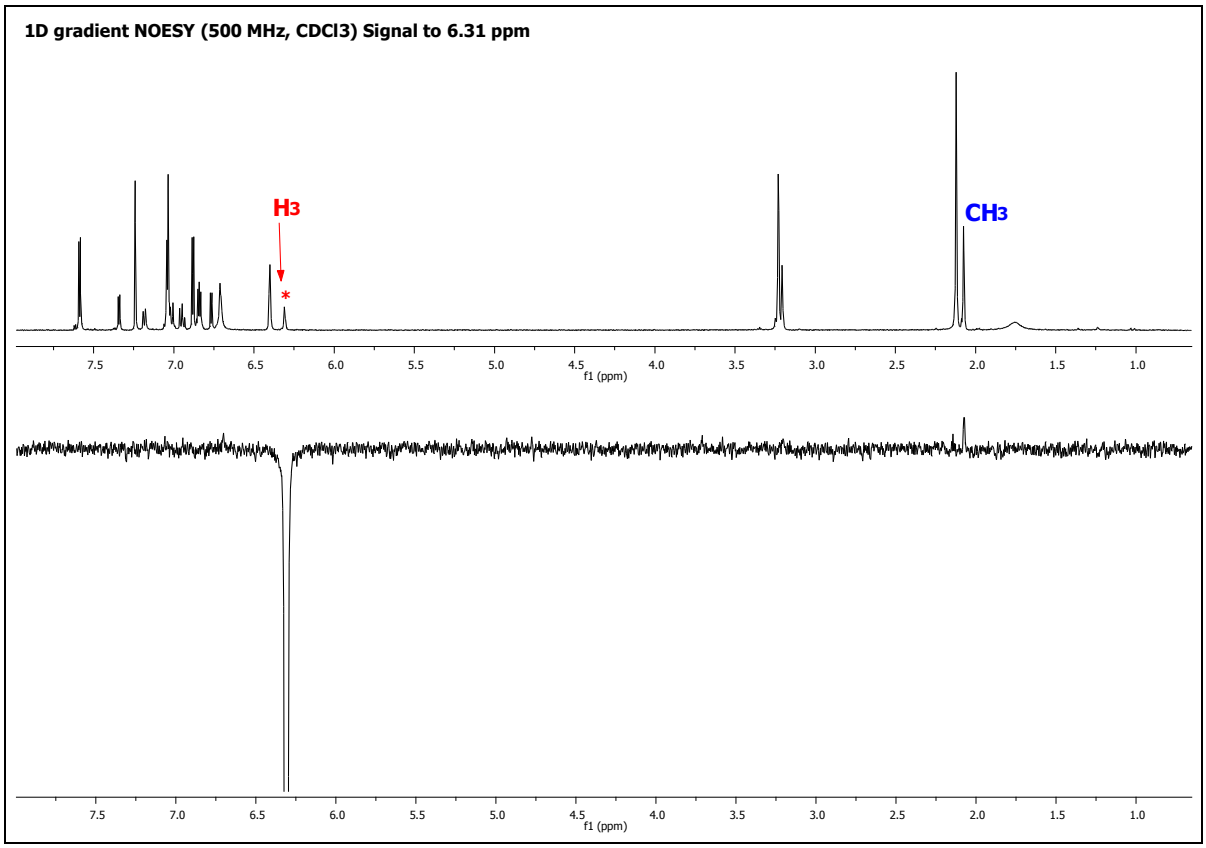


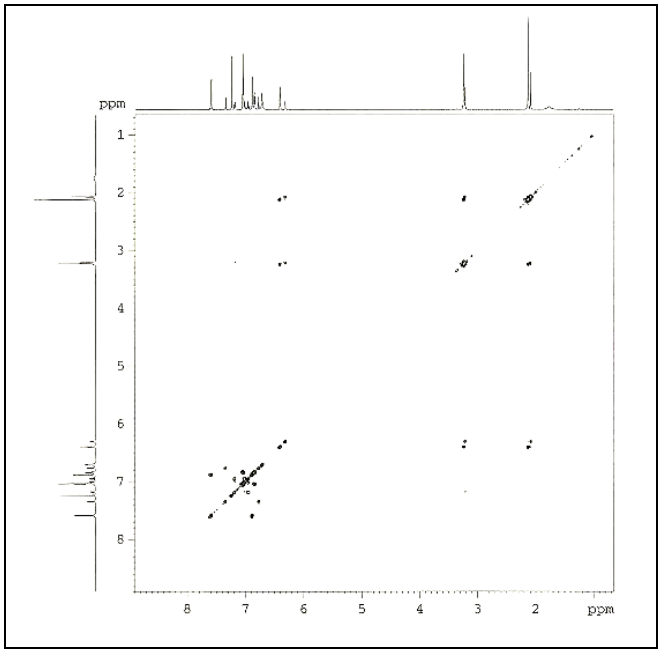
➢ **Compound 49 (major isomer)**



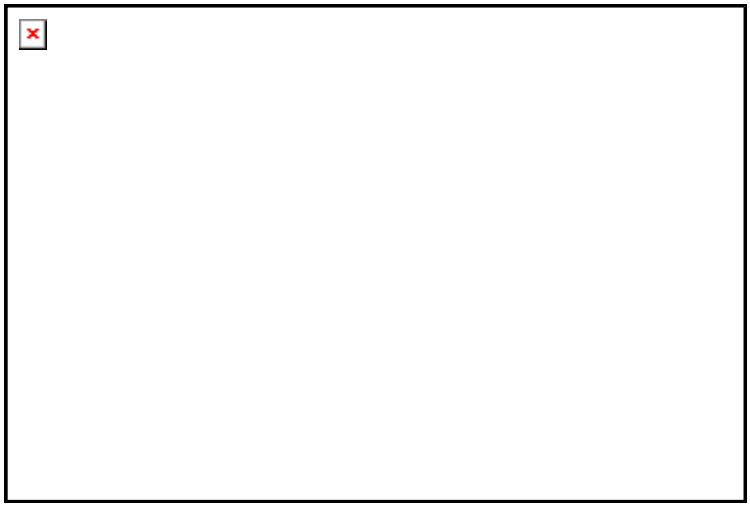

➢ **Compound 50 (minor isomer)**

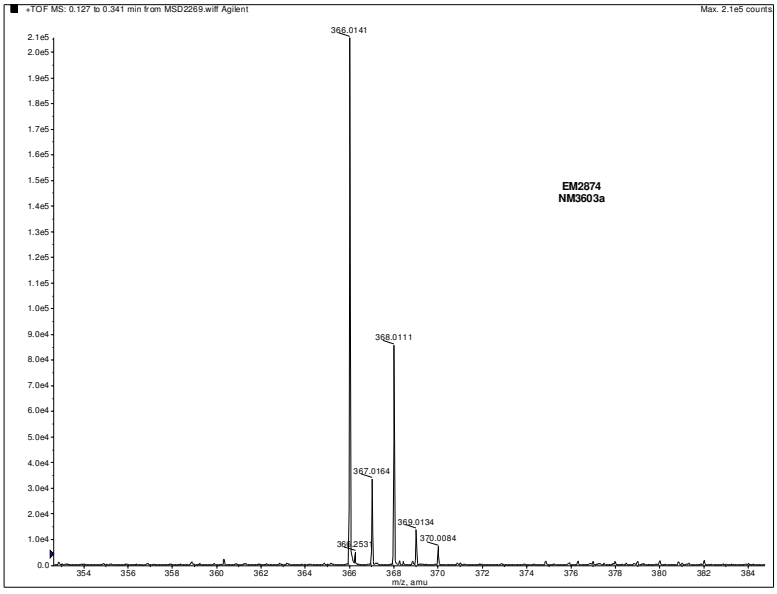


2D gCOSY (500 MHz, $CDCl_3$)

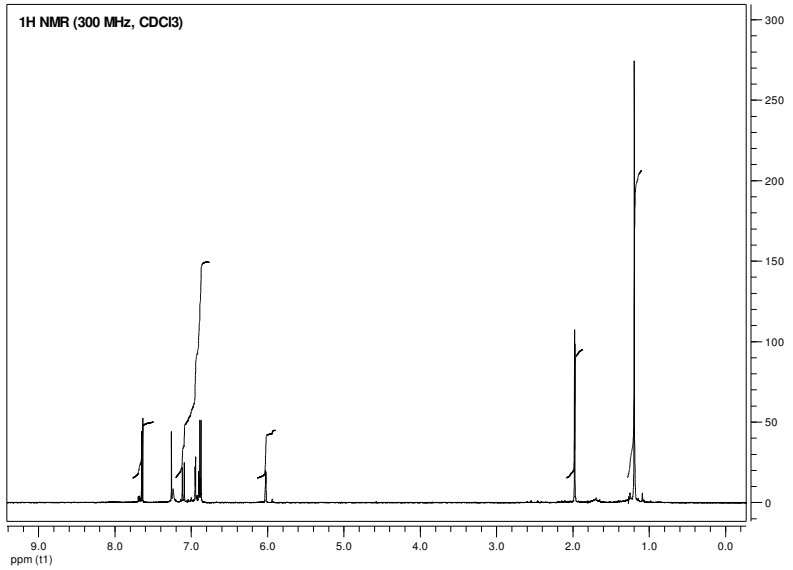


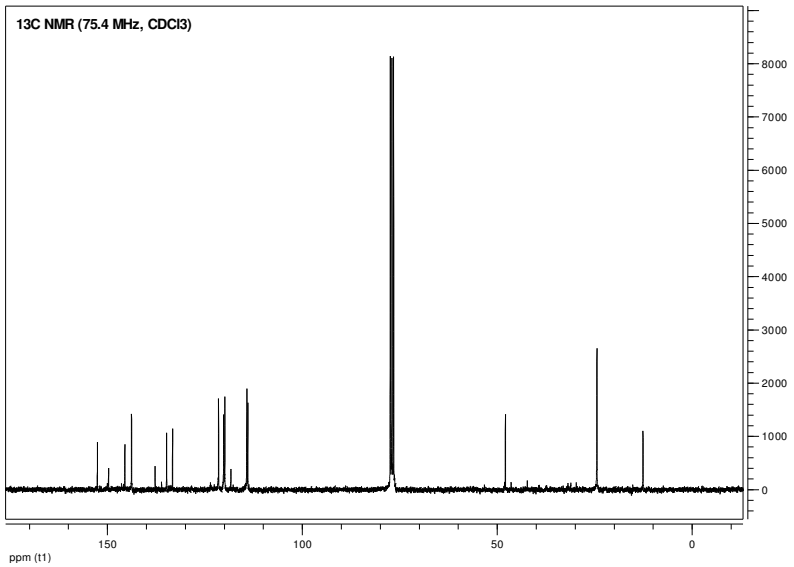

$^{13}C$ NMR (75.4 MHz, $CDCl_3$)

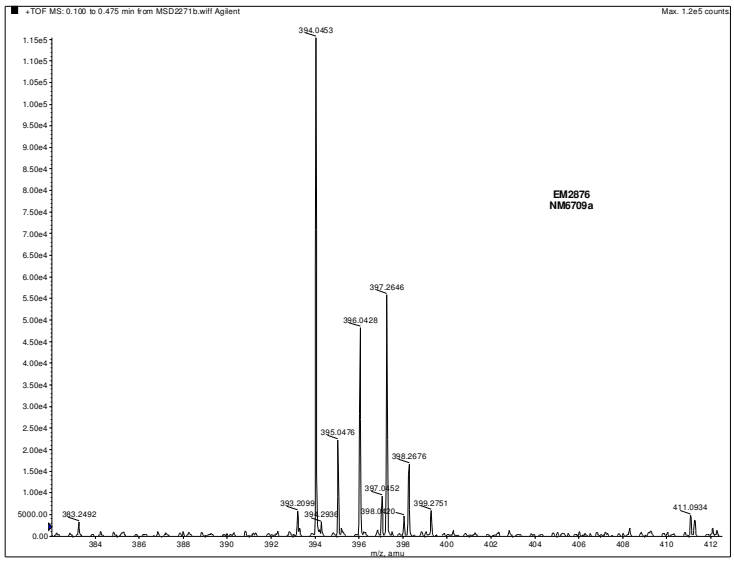




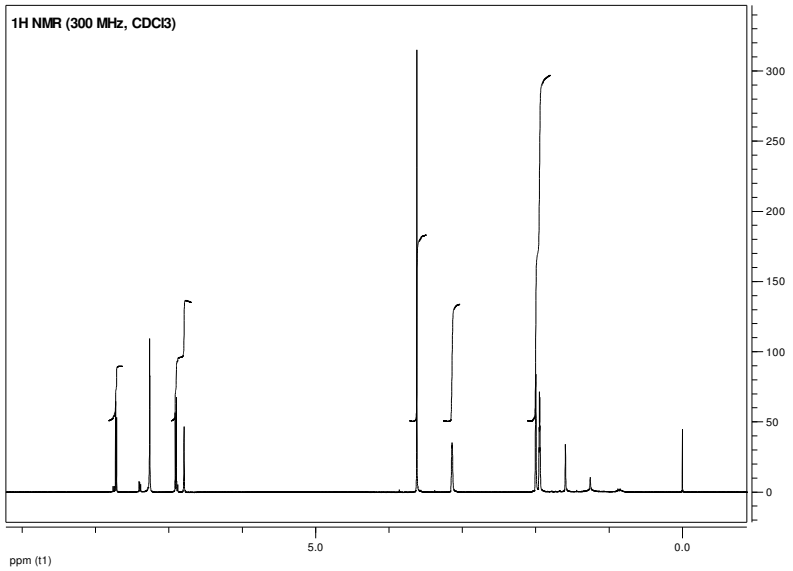
- **6-Chloro-*N*-(1,1,3-trimethyl-1*H*-inden-5-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 51**

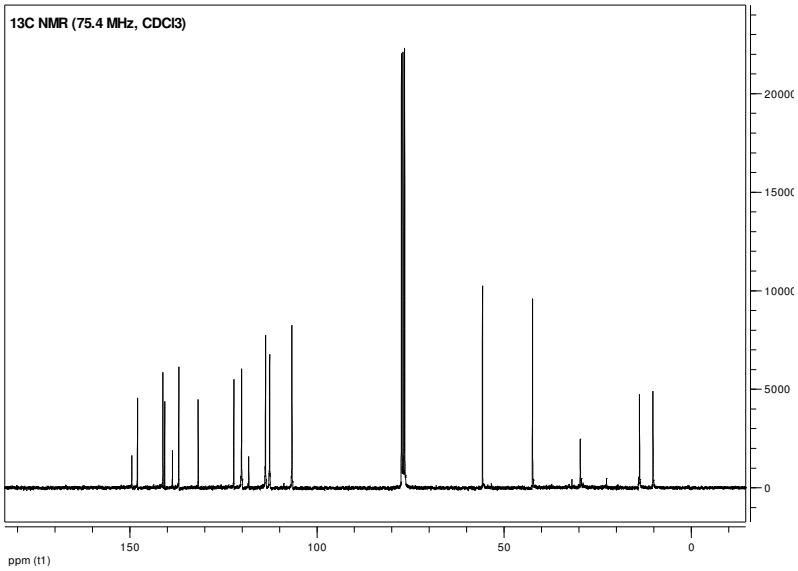


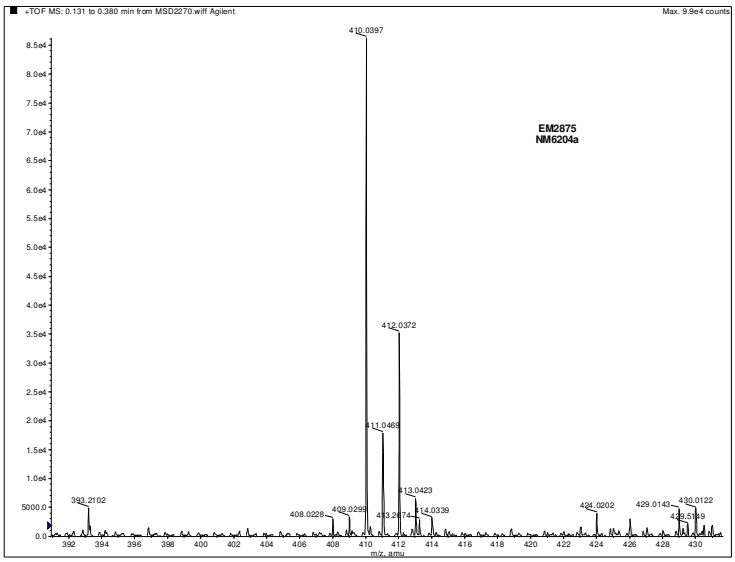



- **6-Chloro-*N*-(6-methoxy-2,3-dimethyl-1*H*-inden-5-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 52**



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Brief Article

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# Identification of Novel Indanylsulfonamide Guanylhydrazones as Potent 5-HT$_6$ Serotonin Receptor Antagonists

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*Received June 3, 2009*

Changing the *N*,*N*-(dimethylamino)ethyl side chain in the *N*-[3-(aminoethyl)inden-5-yl]sulfonamide 5-HT$_6$ serotonin receptor agonists **1** by a conformationally rigid guanylhydrazone moiety at the indene 3-position led to the identification of the title indanylguanylhydrazones **6**, which exhibited excellent binding affinities and an antagonistic response at the 5-HT$_6$ receptor, with $K_i$ and IC$_{50}$ values in the nanomolar range ($K_i \geq 1.2$ nM, IC$_{50} \geq 47$ nM, and $I_{max} \leq 173\%$).



## Introduction

The 5-HT$_6$ serotonin receptor, one of the most recent incorporations to the serotonin receptor family, was isolated from rat striatal messenger ribonucleic acid (mRNA[a]) in 1993 and then identified in humans.[1−3] It is one of the G protein-coupled receptors (GPCRs), and its activation leads to an increase in cyclic adenosine monophosphate (cAMP) production.[2,4,5] In the past few years, the 5-HT$_6$ receptor has became a promising therapeutic target with clinical interest, and recent research has developed a broad array of small molecules acting as potent and selective 5-HT$_6$ antagonists. However, agonists have proved elusive because of their generally modest selectivity.[6−10]

By developing an indole-to-indene switch in the quest for 5-HT$_6$ ligands,[11−13] we have been able to examine several sets of indene-based sulfonamides, the *N*-[3-(aminoethyl)inden-5-yl]sulfonamides **1** and the conformationally rigid counterparts **2**, which show binding affinities with $K_i$ values ≥3 nM (Figure 1). Representative examples of **1**-type ligands are the *N*-(inden-5-yl)imidazothiazole-5-sulfonamides **3** and **4**, which have high affinities and function as potent full agonists for the 5-HT$_6$ receptor ($K_i \geq 4.5$ nM, $E_{max} \geq 98\%$, EC$_{50} \geq 0.3$ nM).[11−13] An example of a **2**-type ligand is the pyrrolidine analogue **5**, which exhibited a high binding affinity ($K_i = 3 \pm 0.3$ nM) although with moderate antagonist potency at micromolar level[13] (Figure 1). Continuing our search for 5-HT$_6$ serotonin receptor ligands, the aim of the present study was to investigate a structural change in the basic amine moiety at the indene 3-position of indenylsulfonamides **1** and **2**. The replacement of the conformationally flexible *N*,*N*-aminoethyl or the rigid cyclic amine side arm by the rigid guanylhydrazone moiety led to the title indanylguanylhydrazone sulfonamides **6**, which showed a high binding affinity with $K_i$ values ≥ 1.2 nM and acted as 5-HT$_6$ receptor antagonists.

In parallel, aminoguanidine hydrazones, displaying interesting pharmaceutical profiles, are suitable structural motifs in a variety of biological agents such as antitumorals,[14,15] antiparasitics,[16] enzyme inhibitors, e.g., 4-amidinoindanone guanylhydrazone (AIGH),[17] cardiotonics,[15a,18] 5-HT$_{2A}$ receptor antagonists (arylguanylhydrazones),[19] and others including those identified by the high throughput screening (HTS) technology.[20] A significant biological response of the guanylhydrazone moiety is its mimicry of the aminoethyl functionality of serotonin (5-HT). In 1995, Mattes and coworkers designed the indolecarbaldehyde guanylhydrazone **7**, which emerged as the prototype of a new class of potent and selective 5-HT$_4$ receptor agonists **8** (Figure 2).[21,22] Recently, Cole et al. examined different indolecarbaldehyde(alkylketone) guanylhydrazones **9** and **10** bearing a sulfonamide group at the indole 5- or 1-position, which exhibited a high binding affinity for the 5-HT$_6$ receptor, e.g. **11**, **12** ($K_i$ = 1.0 nM) and **13**, **14** ($K_i \leq 8.0$ nM), respectively.[23,24] These indolylsulfonamides, **9** and **10**, are guanylhydrazone counterparts of the known arylsulfonyltryptamines exemplified by the agonists **15** (E-6801)[25] and **16** (WAY-181187).[23,26]

**Chemistry.** Several selected examples of **6**-type indanylsulfonamide were synthesized from suitable indanones following the multistep procedures shown in Schemes 1 and 2. Preparation of the guanylhydrazone derivatives started with the sulfonylation of aminoindanone **17** with the appropriate sulfonyl chlorides, giving the corresponding indanone sulfonamides **18**[11] and **19**. Applying the same experimental protocol, reaction of aminoindanones **17**, **20**, **23**, and **25** with 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride afforded indanones sulfonamides **21**, **22**, **24**, and **26**, respectively. Moreover, reduction of nitroindanone **27**[12] afforded aminoindanone **28**, which upon sulfonylation gave indanone imidazothiazolesulfonamide **29**. On the other hand, *N*-alkylation of **21** provided *N*-methyl-*N*-indenylsulfonamide **30** (Scheme 1).

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[a] Abbreviations: 5-HT, serotonin; mRNA, messenger ribonucleic acid; GPCRs, G protein-coupled receptors cAMP, cyclic adenosine monophosphate; AIGH, 4-amidinoindanone guanylhydrazone; HTS, high throughput screening; SERT, serotonin transporter; HEK, human embryo kidney; HTRF, homogeneous time-resolved fluorescence; [$^3$H]-LSD, tritiated lysergic acid diethylamide.



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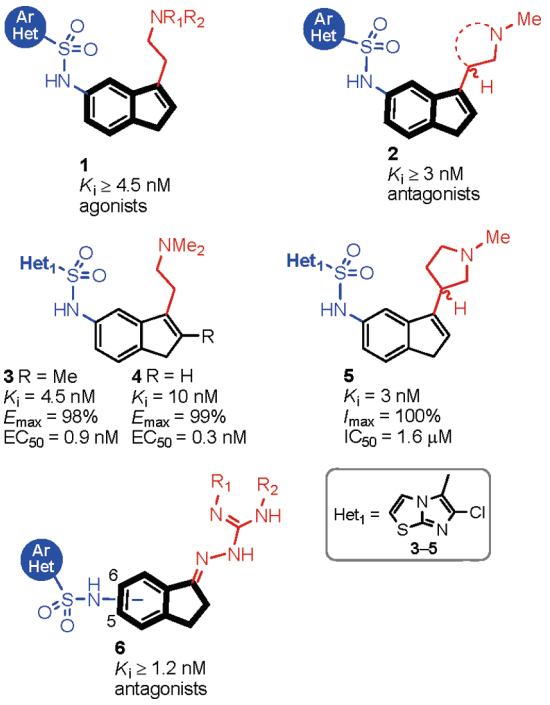



**Figure 1.** Indene-based frameworks targeting the 5-$HT_6$ serotonin receptor.

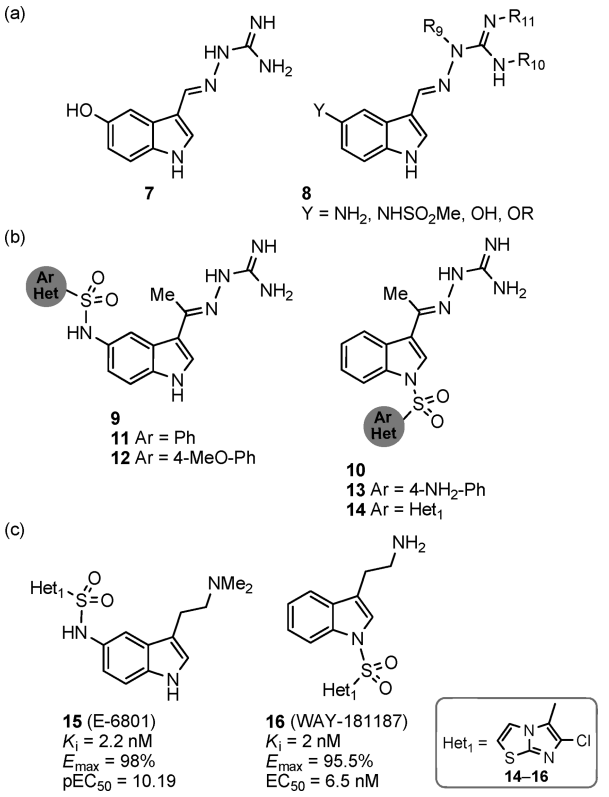



**Figure 2.** Indole guanylhydrazones and the 5-HT serotonin receptor family: (a) 5-$HT_4$ prototype **7** and **8**-type ligands; (b) 5-$HT_6$ indolylsulfonamide guanylhydrazones **9** and **10**, e.g. **11**−**14**; (c) 5-$HT_6$ arylsulfonyltryptamine counterparts represented by agonists **15** and **16**.

The targeted indanylguanylhydrazone sulfonamides were prepared by reaction between the corresponding indanone sulfonamides and the appropriate hydrazine derivatives under acidic conditions. Therefore, condensation of sulfonamides **18** and **19** with a suspension of aminoguanidine hydrochloride, the latter prepared in turn from a suspension of aminoguanidine bicarbonate and an excess of hydrochloric acid, provided indanylsulfonamide guanylhydrazones **31** and **32**, respectively. Furthermore, reaction of compound **19** with 2-hydrazino-2-imidazoline hydrobromide in refluxing ethanol/HCl gave the cyclic indanylguanylhydrazone sulfonamide **33** (Scheme 2 and Scheme S1 of SI).

Following the same experimental procedure, condensation of indanone imidazothiazolesulfonamides **21**, **22**, **24**, **26**, **29**, and **30** with aminoguanidine hydrochloride afforded indanylsulfonamide guanylhydrazones **34**, the racemic **35**, and **36**−**39**, respectively. Finally, reaction of compounds **21** and **29** with 2-hydrazino-2-imidazoline hydrobromide in refluxing EtOH/HCl provided cyclic indanylguanylhydrazone sulfonamides **40** and **41**, respectively (Scheme 2 and Scheme S1 of SI).

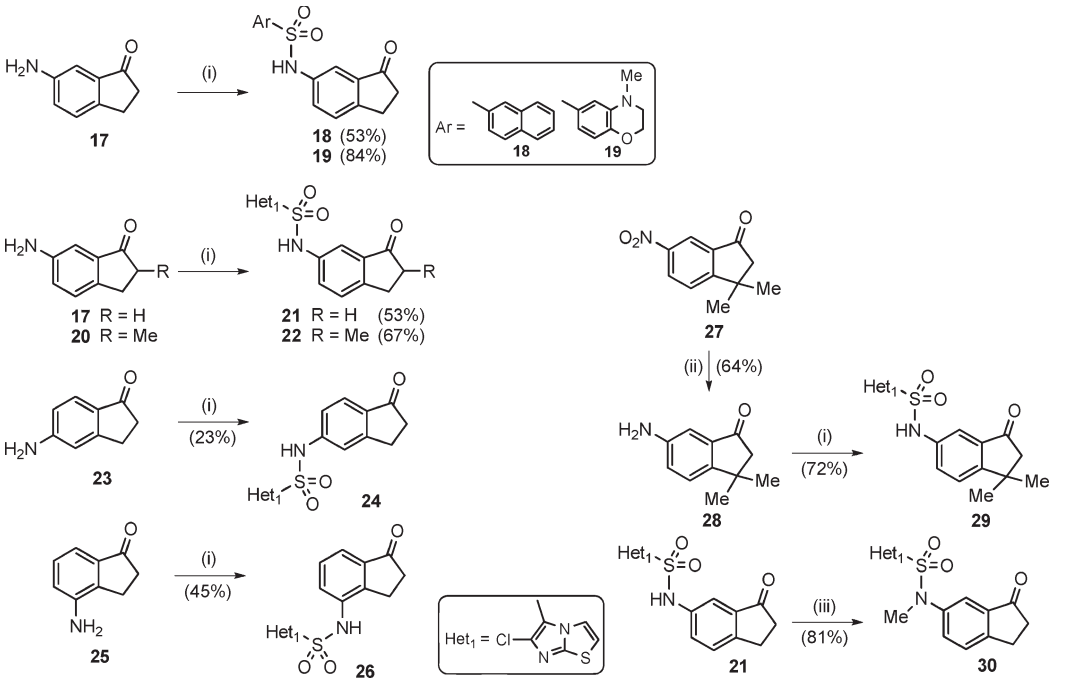
Pure indanylguanylhydrazone sulfonamides were isolated as solids after crushing the evaporated reaction mixture with a suitable solvent. The structure of the new compounds was confirmed by spectroscopic methods. Their $^1$H NMR and $^{13}$C NMR chemical shifts and physical data are gathered in the Experimental Section (see Table 1 and Supporting Information (SI)). The $^1$H NMR spectra of guanylhydrazone hydrochlorides **31**, **32**, and **34**−**39** recorded in DMSO-$d_6$ at 300 MHz are in agreement with the assigned structures: for the guanylhydrazone moiety, a singlet at ∼11 ppm corresponding to one NH group, and a broad signal at ∼8 ppm, corresponding to the guanyl group. Moreover, on the basis of a 1D NOESY experiment at 500 MHz in DMSO-$d_6$, it was inferred that the C=N− bond of **35** belonged to an *E*-isomer structure because irradiation of the methyl group led to an enhancement of both =N−NH− and $-CH_2-$ (Figure S1, SI).

## Results and Discussion

An array of *N*-[3-(aminoethyl)inden-5-yl]sulfonamides **1** have been previously reported as part of our research work on indene-based ligands for the 5-$HT_6$ receptor, including the potent agonists **4** and **5**.[11−13] Having substituted the *N*,*N*-(dimethylamino)ethyl side chain in sulfonamides **1** by a guanylhydrazone moiety, we focused our attention to examples of **6**-type sulfonamide guanylhydrazones[27] and the targeted compounds **31**−**41** were selected on the basis of previously established structural requirements for enhancing the affinity of indene-based scaffolds toward the 5-$HT_6$ receptor, especially the aryl(heteroaryl)portion of the sulfonamide functionality (e.g., the 6-chloroimidazo[2,1-*b*]thiazole motif).[11,12] Selected indanylsulfonamide guanylhydrazones **31**−**41** were tested in a standard radioligand competition binding assay,[28] using membranes of human embryo kidney cells (HEK-293) expressing the human 5-$HT_6$ recombinant receptor, and were found to exhibit affinities with $K_i$ values ≥1.2 nM (Table 1). The substitution of a 2-naphthyl nucleus in **31** ($K_i$ = 62 ± 29 nM) by a 4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine motif lowered the $K_i$ value to 26 nM for compound **32**. However, conversion of the guanylhydrazone group to the imidazolinylhydrazone **33** resulted in a ∼3-fold loss in activity relative to **32**.

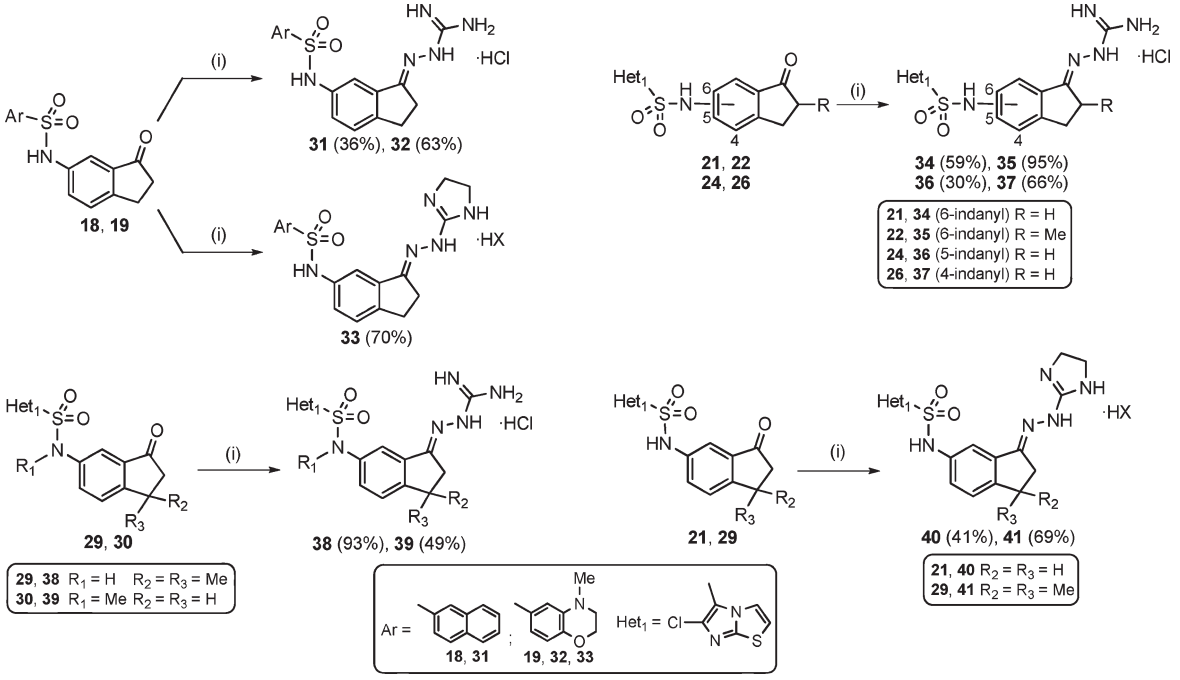
The affinity was enhanced upon introduction of the 6-chloroimidazo[2,1-*b*][1,3]thiazole structural motif, with compounds **34** ($K_i$ = 1.2 ± 0.6 nM) and the racemic **35** ($K_i$ = 1.6 ± 0.1 nM) exhibiting the best binding affinities at the 5-$HT_6$ receptor. Moving the sulfonamide group from the indane 6-position to the 5-position hardly changed the binding affinity. Comparing the affinities of the isomers 6-sulfonylaminoindanyl

**Scheme 1**[a]




[a] Reagents and conditions: (i) Ar(Het)$SO_2Cl$, pyridine, rt; (ii) Fe, AcOH-$H_2O$, 90 °C; (iii) (a) $K_2CO_3$, dry DMF, rt, (b) MeI, rt.

**Scheme 2**[a]

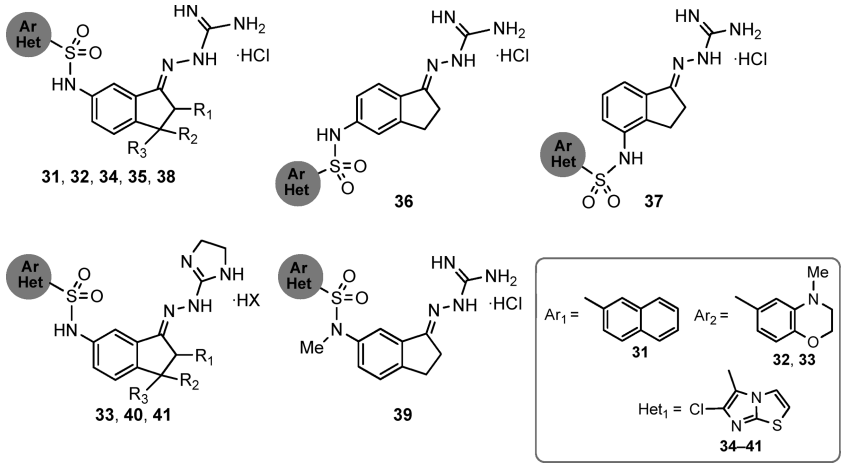



[a] Reagents and conditions: (i) aminoguanidine hydrogencarbonate or 2-hydrazino-4,5-dihydro-1*H*-imidazole hydrobromide, 37% HCl, solvent, reflux.

**34** ($K_i = 1.2 \pm 0.6$ nM), 5-sulfonylaminoindanyl **36** ($K_i = 2.6 \pm 0.5$ nM), and 4-sulfonylaminoindanyl **37** (inhibition of 2% at 100 nM) permitted us to rule out additional studies with compounds containing a sulfonamide moiety at the indane 4-position. Additional studies with compounds bearing a 3,3-dimethylindane core, such as **38** ($K_i = 5.2 \pm 0.4$ nM), or a *N*-methyl sulfonamide group, such as **39** ($K_i = 4.1 \pm 0.2$ nM), showed ~ 3-fold weaker affinities compared to compound **34**. Yet when the guanylhydrazone pattern was changed by an imidazolinylhydrazone group, compound **40** ($K_i = 2.2 \pm 0.3$ nM) gave a similar affinity to **34** (Figure S2, SI). Interestingly, the indanylsulfonamides **34**−**36** and **40** displayed a similar high 5-$HT_6$ affinity to the **1**-type indenysulfonamides, e.g. **3** ($K_i = 4.5 \pm 1.9$ nM),[12] and to the **9**-type indolylsulfonamide, e.g. **11** and **12** ($K_i = 1.0$ nM).[24]

To establish the correlation between receptor affinity and functional activity, efficacy of these ligands was determined in a cAMP homogeneous time-resolved fluorescence (HTRF) assay format in HEK-293F cells stably expressing the human 5-$HT_6$ receptor.[29−31] Guanylhydrazones **31**−**41** inhibited

**Table 1.** Physical Data, 5-HT$_6$ Receptor Affinity, and Functionality of Compounds **5** and **31**−**41**




| compd | $R_1$ | $R_2$, $R_3$ | Ar/Het | precursor | yield (%)[a] | mp (°C)[a] | $K_i$ (nM)[b,c] | $I_{max}$ (%)[b,d] | $IC_{50}$ (nM)[b,d] |
|---|---|---|---|---|---|---|---|---|---|
| **5**[e] | | | $Het_1$ | | | | 3 ± 0.3 | 100 ± 3 | 1580 ± 40 |
| **31** | | | $Ar_1$ | **18** | 36 | 256−257 | 62 ± 29 | 127 ± 9 | 53 ± 9 |
| **32** | | | $Ar_2$ | **19** | 63 | 190−191 | 26 ± 8 | 187 ± 37 | 581 ± 16 |
| **33** | | | $Ar_2$ | **19** | 70 | 264−265 | 70 ± 12 | nd[f] | nd |
| **34** | | | $Het_1$ | **21** | 59 | 219−220 | 1.2 ± 0.6 | 127 ± 9 | 96 ± 25 |
| **35**[f] | Me | | $Het_1$ | **22** | 95 | >300 | 1.6 ± 0.1 | 157 ± 6 | 58 ± 9 |
| **36** | | | $Het_1$ | **24** | 30 | 249−250 | 2.6 ± 0.5 | 173 ± 25 | 47 ± 5 |
| **37**[g] | | | $Het_1$ | **26** | 66 | >300 | nd | nd | nd |
| **38** | | Me | $Het_1$ | **29** | 93 | 225−226 | 5.2 ± 0.4 | 146 ± 12 | 238 ± 32 |
| **39** | | | $Het_1$ | **30** | 49 | 253−254 | 4.1 ± 0.2 | 102 ± 9 | 54 ± 7 |
| **40** | | | $Het_1$ | **21** | 41 | 245−246 | 2.2 ± 0.3 | 173 ± 45 | 176 ± 69 |
| **41**[h] | | Me | $Het_1$ | **29** | 69 | >300 | nd | nd | nd |

[a] Compounds **31**, **32**, **34**−**39** were prepared as hydrochloride salts, and compounds **33**, **40** and **41** could be a mixture of hydrohalide salts. [b] Data are the mean ± SEM of three experiments. [c] $K_i$ was calculated when inhibition at 100 nM > 80%. [d] Antagonism was expressed as $I_{max}$ and $IC_{50}$ values. [e] See ref 13. [f] Racemic mixture. [g] Inhibition of 2% at 100 nM. [h] Inhibition of 77% at 100 nM. [I] nd, not determined.

5-HT stimulated cAMP production with $IC_{50}$ values ≥47 nM and $I_{max}$ values in the range of 102−173%. It was also interesting to observe that compounds **31**−**41** were more potent antagonists than the conformationally rigid **2**-type indenylsulfonamides, e.g. **5** with $I_{max}$ = 100 ± 3% and $IC_{50}$ = 1.6 ± 0.4 μM (Table 1). The binding affinities of **31**, **32**, and **34**−**40** for a panel of several serotonin and adrenergic receptors as well as the serotonin transporter (SERT) were negligible (Table S1, SI).

## Conclusions

In our continued search for 5-HT$_6$ serotonin receptor ligands related to the disubstituted *N*-[3-(aminoethyl)inden-5-yl]sulfonamide agonists **1**, the present study was designed to examine a structural change of the basic amine moiety at the indene 3-position. The replacement of the conformationally flexible *N*,*N*-(dimethylamino)ethyl side chain by a rigid guanylhydrazone moiety led to the identification of novel indanylsulfonamide guanylhydrazones **6** with excellent binding affinities at the 5-HT$_6$ receptor ($K_i$ ≥ 1.2 nM). In a functional adenylyl cyclase assay, **6**-type ligands behaved as full 5-HT$_6$ receptor antagonists showing values of $IC_{50}$ ≥ 47 nM and $I_{max}$ ≤ 173%, with negligible activities against several serotoninergic and adrenergic receptors as well as the SERT. Among them, compounds **34** and **35** displayed the finest biological profile.

## Experimental Section

**Chemistry.** General methods, materials, full experimental details, and structural characterization of all compounds are reported in the SI. We describe herein the general procedure for the preparation of the final products. For targeted compounds, satisfactory high-resolution mass spectra and HPLC analyses were obtained, confirming >95% purity.

**Synthesis of Indanylsulfonamide Guanylhydrazones 31**−**41. General Procedure.** To a solution of indanone sulfonamides **18**, **19**, **21**, **22**, **24**, **26**, **29**, and **30** (1.0 equiv) in the suitable solvent was added a suspension of aminoguanidine hydrogencarbonate or 2-hydrazino-4,5-dihydro-1*H*-imidazole hydrobromide (1.1 equiv) in an excess of hydrochloric acid, and the mixture was heated to reflux for 18 h. The reaction mixture was cooled in an ice bath to obtain a solid that was isolated by filtration or the crude reaction was evaporated to dryness and was purified by crushing with a suitable solvent.

**5-HT$_6$ Binding Assay.** Affinity of compounds at 5-HT$_6$ receptors was evaluated utilizing membranes from HEK-293 cells with human 5-HT$_6$ serotonin receptor expressed and tritiated lysergic acid diethylamide ([$^3$H]-LSD) as the radioligand[28] (see SI).

**Adenylyl Cyclase Activity Assay.** Functional effects of the compounds were evaluated by cAMP measurements on HEK-293F cells stably expressing the human 5-HT$_6$ receptor using a HTRF assay format (see SI).[29−31]

**Acknowledgment.** This research was supported by ESTEVE, Barcelona, Spain, through projects FBG2004/05-302663 and FBG2006/07-303647 Fundació Bosch i Gimpera-Universitat de Barcelona, Spain. S.L.-P. thanks ESTEVE for a graduate fellowship (2004-07) and the AGAUR for a predoctoral 2008-F.I. fellowship. Thanks are also due to the AGAUR, Grup de Recerca Consolidat 2005SGR158 and 2009SGR562.

**Supporting Information Available:** Full experimental conditions and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

## References


(1) Monsma, F. J., Jr.; Shen, Y.; Ward, R. P.; Hamblin, M. W.; Sibley, D. R. Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol. Pharmacol.* **1993**, *43*, 320−327 and references cited.

(2) Ruat, M.; Traiffort, E.; Arrang, J. M.; Tardivel-Lacombe, J.; Diaz, J.; Leurs, R.; Schwartz, J. C. A novel rat serotonin (5-$HT_6$) receptor: molecular cloning, localization and stimulation of cAMP accumulation. *Biochem. Biophys. Res. Commun.* **1993**, *193*, 268–276.

(3) Kohen, R.; Metcalf, M. A.; Khan, N.; Druck, T.; Huebner, K.; Lachowicz, J. E.; Meltzer, H. Y.; Sibley, D. R.; Roth, B. L.; Hamblin, M. W. Cloning, characterization, and chromosomal localization of a human 5-$HT_6$ serotonin receptor. *J. Neurochem.* **1996**, *66*, 47–56.

(4) Sebben, M.; Ansanay, H.; Bockaert, J.; Dumuis, A. 5-$HT_6$ receptors positively coupled to adenylyl cyclase in striatal neurones in culture. *NeuroReport* **1994**, *5*, 2553–2557.

(5) Sleight, A. J.; Boess, F. G.; Bos, M.; Bourson, A. The putative 5-$HT_6$ receptor: localization and function. *Ann. N. Y. Acad. Sci.* **1998**, *861*, 91–96.

(6) Glennon, R. A. Higher-End serotonin receptors: 5-$HT_5$, 5-$HT_6$, and 5-$HT_7$. *J. Med. Chem.* **2003**, *46*, 2795–2812.

(7) Nichols, D. E.; Nichols, C. D. Serotonin Receptors. *Chem. Rev.* **2008**, *108*, 1614–1641.

(8) Johnson, C. N.; Ahmed, M.; Miller, Neil, D. 5-$HT_6$ receptor antagonists: prospects for the treatment of cognitive disorders including dementia. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 642–654.

(9) Heal, D. J.; Smith, S. L.; Fisas, A.; Codony, X.; Buschmann, H. Selective 5-$HT_6$ receptor ligands: progress in the development of a novel pharmacological approach to the treatment of obesity and related metabolic disorders. *Pharmacol. Ther.* **2008**, *117*, 207–231.

(10) Liu, K. G.; Robichaud, A. J. 5-$HT_6$ Antagonists as potential treatment for cognitive dysfunction. *Drug Dev. Res.* **2009**, *70*, 145–168.

(11) Alcalde, E.; Mesquida, N.; Frigola, J.; López-Pérez, S.; Mercè, R. Indene-based scaffolds. Design and synthesis of novel serotonin 5-$HT_6$ receptor ligands. *Org. Biomol. Chem.* **2008**, *6*, 3795–3810.

(12) Alcalde, E.; Mesquida, N.; López-Pérez, S.; Frigola, J.; Mercè, R. An Indole−Indene Switch: Discovery of Novel Indenylsulfonamides as 5-$HT_6$ Serotonin Receptor Agonists. *J. Med. Chem.* **2009**, *52*, 675–687.

(13) Frigola, J.; Mercè, R.; Holenz, J.; Alcalde, E.; Mesquida, N.; López-Pérez, S. Preparation of indene derivatives for treatment of 5-HT6 receptors mediated diseases. World Patent WO 07/054257 A2, CAN 146:521555, **2007**.

(14) Andreani, A.; Rambaldi, M.; Locatelli, A.; Bossa, R.; Fraccari, A.; Galatulast, I. Potential Antitumor Agents. 21. Structure Determination and Antitumor Activity of Imidazo[2,1-*b*]thiazole Guanylhydrazones. *J. Med. Chem.* **1992**, *35*, 4634–4637.

(15) (a) Andreani, A.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Recanatini, M.; Garaliene, V. Potential Antitumor Agents. Part 29: Synthesis and Potential Coanthracyclinic Activity of Imidazo[2,1-*b*]thiazole Guanylhydrazones. *Biorg. Med. Chem.* **2000**, *8*, 2359−2366 and references cited. (b) Andreani, A.; Burnelli, S.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Calonghi, N.; Cappadone, C.; Farruggia, G.; Zini, M.; Stefanelli, C.; Masotti, L.; Radin, N. S.; Shoemaker, R. H. New Antitumor Imidazo[2,1-b]thiazole Guanylhydrazones and Analogues. *J. Med. Chem.* **2008**, *51*, 809−816 and references cited.

(16) Papanastasiou, I.; Tsotinis, A.; Kolocouris, N.; Prathalingam, S. R.; Kelly, J. M. Design, Synthesis, and Trypanocidal Activity of New Aminoadamantane Derivatives. *J. Med. Chem.* **2008**, *51*, 1496–1500.

(17) Stanek, J.; Caravatti, G.; Frei, J.; Furet, P.; Mett, H.; Schneider, P.; Regenass, U. 4-Amidinoindan-l-one 2′-Amidinohydrazone: A New Potent and Selective Inhibitor of *S*-Adenosylmethionine Decarboxylase. *J. Med. Chem.* **1993**, *36*, 2168–2171.

(18) Melero, C. P.; Sevillano, L. G.; Caballero, E.; Tomé, F.; Carrón, R.; Montero, M. J.; San Feliciano, A.; Medarde, M. Hydroindenic-guanylhydrazones. Synthesis and evaluation as Inotropic Agents. *Biorg. Med. Chem. Lett.* **1998**, *8*, 3217–3222.

(19) Bryant, H. U.; Nelson, D. L.; Button, D.; Cole, H. W.; Baez, M. B.; Lucaites, L.; Wainscott, D. B.; Whitesitt, C.; Reel, J.; Simon, R.; Koppel, G. A. A novel class of 5-$HT_4$ receptor antagonists: aryl aminoguanidines. *Life Sci.* **1996**, *59*, 1259–1268.

(20) (a) Khownium, K.; Wood, S. J.; Miller, K. A.; Balakrishna, R.; Nguyen, T. B.; Kimbrell, M. R.; Georg, G. I.; David, S. A. Novel endotoxin-sequestering compounds with terephthalaldehyde-bis-guanylhydrazone scaffolds. *Biorg. Med. Chem. Lett.* **2006**, *16*, 1305–1308. (b) Wei, R. G.; Arnaiz, D. O.; Chou, Y.-L.; Davey, D.; Dunning, L.; Lee, W.; Lu, S.-F.; Onuffer, J.; Ye, B.; Phillips, G. CCR5 receptor antagonists: Discovery and SAR study of guanylhydrazone derivatives. *Biorg. Med. Chem. Lett.* **2007**, *17*, 231–234.

(21) Buchheit, K.-H.; Gamse, R.; Giger, R.; Hoyer, D.; Klein, F.; Kloppner, E.; Pfannkuche, H.-J.; Mattes, H. The Serotonin 5-$HT_4$ Receptor. 1. Design of a New Class of Agonists and Receptor Map of the Agonist Recognition Site. *J. Med. Chem.* **1995**, *38*, 2326−2330 and references cited.

(22) Buchheit, K.-H.; Gamse, R.; Giger, R.; Hoyer, D.; Klein, F.; Kloppner, E.; Pfannkuche, H.-J.; Mattes, H. The Serotonin 5-$HT_4$ Receptor. 2. Structure−Activity Studies of the Indole Carbazimidamide Class of Agonists. *J. Med. Chem.* **1995**, *38*, 2331–2338.

(23) Cole, D. C.; Stock, J. R.; Lennox, W. J.; Bernotas, R. C.; Ellingboe, J. W.; Boikess, S.; Coupet, J.; Smith, D. L.; Leung, L.; Zhang, G.-M.; Feng, X.; Kelly, M. F.; Galante, R.; Huang, P.; Dawson, L. A.; Marquis, K.; Rosenzweig-Lipson, S.; Beyer, C. E.; Schechter, L. E. Discovery of $N_1$-(6-Chloroimidazo[2,1-*b*][1,3]-thiazole-5-sulfonyl)tryptamine as a potent, selective, and orally active 5-$HT_6$ receptor agonist. *J. Med. Chem.*, **2007**, *50*, 5535−5538.

(24) (a) Cole, D. C.; Kelly, M. G.; Bravo, B. A.; Palmer, Y. L. (1-Substituted-indol-3-yl)alkylidenehydrazinecarboximidamide derivatives as 5-hydroxytryptamine-6 ligands. US Patent US 2003/0232843 A1, CAN 140:27762, **2003**. (b) Cole, D. C.; Kelly, M. G.; Nunn, D. S.; Greenblatt, L. P. Indolylalkylidenehydrazinecarboximidamide derivatives as 5-hydroxytryptamine-6 ligands. US Patent US 2004/0002527 A1, CAN 140:77025, **2004**.

(25) (a) Mercè, R.; Andaluz, B.; Frigola, J. Sulphonamide derivatives, their preparation thereof and the application of same as medicaments. World Patent WO 03/042175 A1, CAN 138:401602, **2003**. (b) Holenz, J.; Mercè, R.; Díaz, J. L.; Guitart, X.; Codony, X.; Dordal, A.; Romero, G.; Torrens, A.; Mas, J.; Andaluz, B.; Hernández, S.; Monroy, X.; Sánchez, E.; Hernández, E.; Pérez, R.; Cubí, R.; Sanfeliu, O.; Buschmann, H. Medicinal chemistry driven approaches toward novel and selective serotonin 5-$HT_6$ receptor ligands. *J. Med. Chem.* **2005**, *48*, 1781–1795.

(26) Schechter, L. E.; Lin, Q.; Smith, D. L.; Zhang, G.; Shan, Q.; Platt, B.; Brandt, M. R.; Dawson, L. A.; Cole, D.; Bernotas, R.; Robichaud, A.; Rosenzweig-Lipson, S.; Beyer, C. E. Neuropharmacological profile of novel and selective 5-$HT_6$ receptor agonists: WAY-181187 and WAY-208466. *Neuropsychopharmacology* **2007**, 1–13.

(27) Alcalde, E.; Mesquida, N.; López-Pérez, S.; Frigola, J.; Mercè, R.; Holenz, J.; Substituted indanyl sulfonamide compounds, their preparation ans use as medicaments. World Patent WO 08/015137 A2, CAN 148:191738, **2008**.

(28) (a) Roth, B. L.; Craigo, S. C.; Choudhary, M. S.; Uluer, A.; Monsma, F. J., Jr.; Shen, Y.; Meltzer, H. Y.; Sibley, D. R. Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 1403–1410. (b) Munson, P. J.; Rodbard, D. LIGAND: A versatile, computerized approach for characterization of ligand-binding systems. *Anal. Biochem.* **1980**, *107*, 220–239.

(29) Fisas, A.; Codony, X.; Romero, G.; Dordal, A.; Giraldo, J.; Mercè, R.; Holenz, J.; Heal, D.; Buschmann, H.; Pauwels, P. J. Chronic 5-$HT_6$ receptor modulation by E-6837 induces hypophagia and sustained weight loss in diet-induced obese rats. *Br. J. Pharmacol.* **2006**, *148*, 973–983.

(30) Romero, G.; Sánchez, E.; Pujol, M.; Pérez, P.; Codony, X.; Holenz, J.; Buschmann, H.; Pauwels, P. J. Efficacy of selective 5-$HT_6$ receptor ligands determined by monitoring 5-$HT_6$ receptor-mediated cAMP signaling pathways. *Br. J. Pharmacol.* **2006**, *148*, 1133–1143.

(31) Romero, G.; Pujol, M.; Pérez, P.; Buschmann, H.; Pauwels, P. J. Whole spectrum analysis of ligand efficacy at constitutively active human wild-type and S267K 5-$HT_6$ receptors in HEK-293F cells. *J. Pharmacol. Toxicol. Methods* **2007**, *55*, 144–150.

# Supporting Information

## Identification of Novel Indanylsulfonamide Guanylhydrazones as Potent 5-HT$_6$ Serotonin Receptor Antagonists

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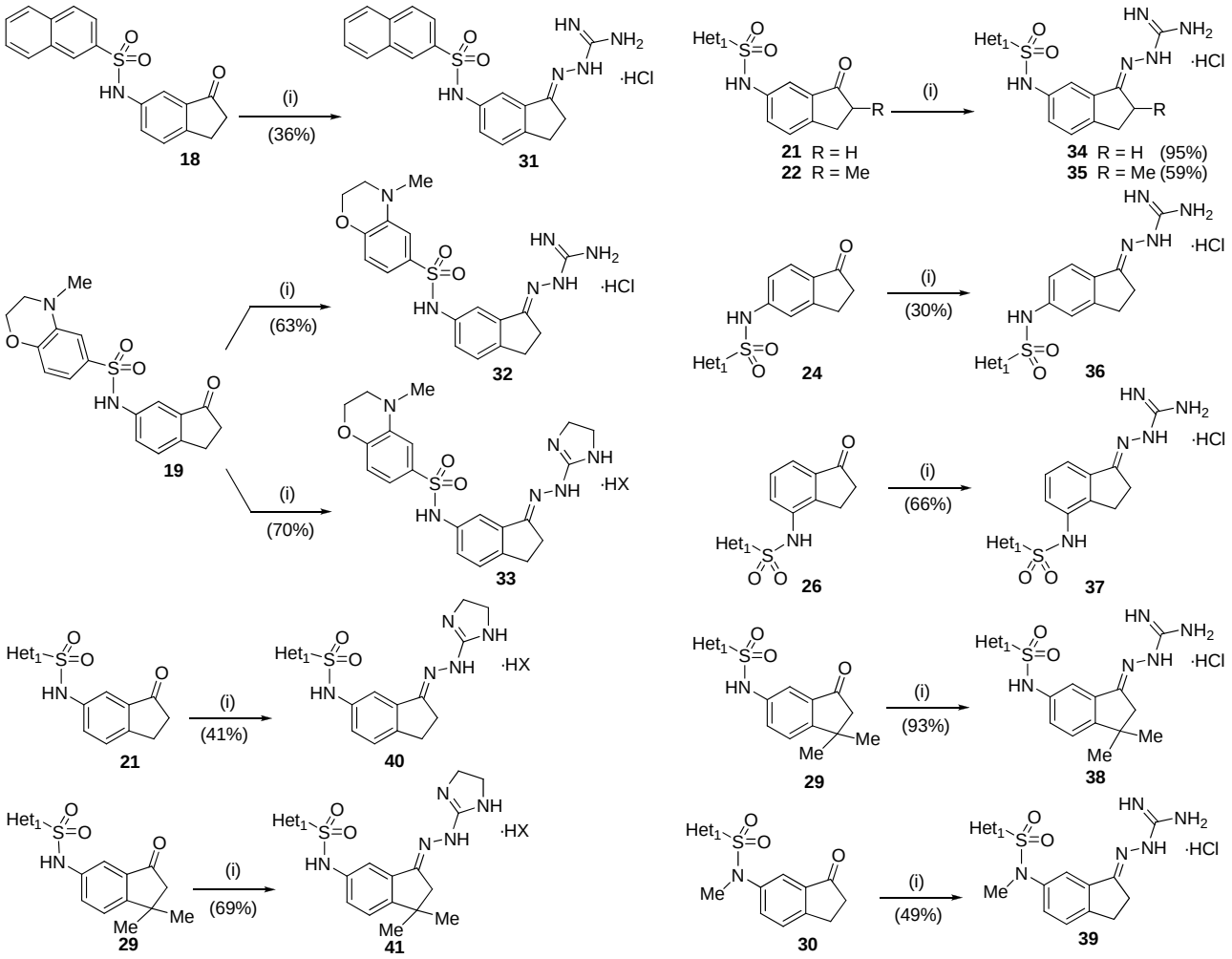
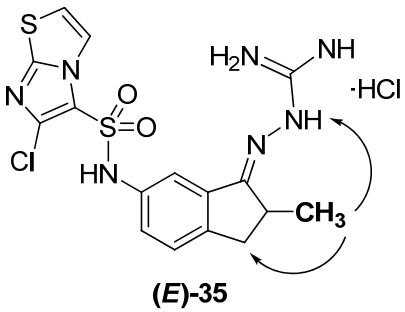


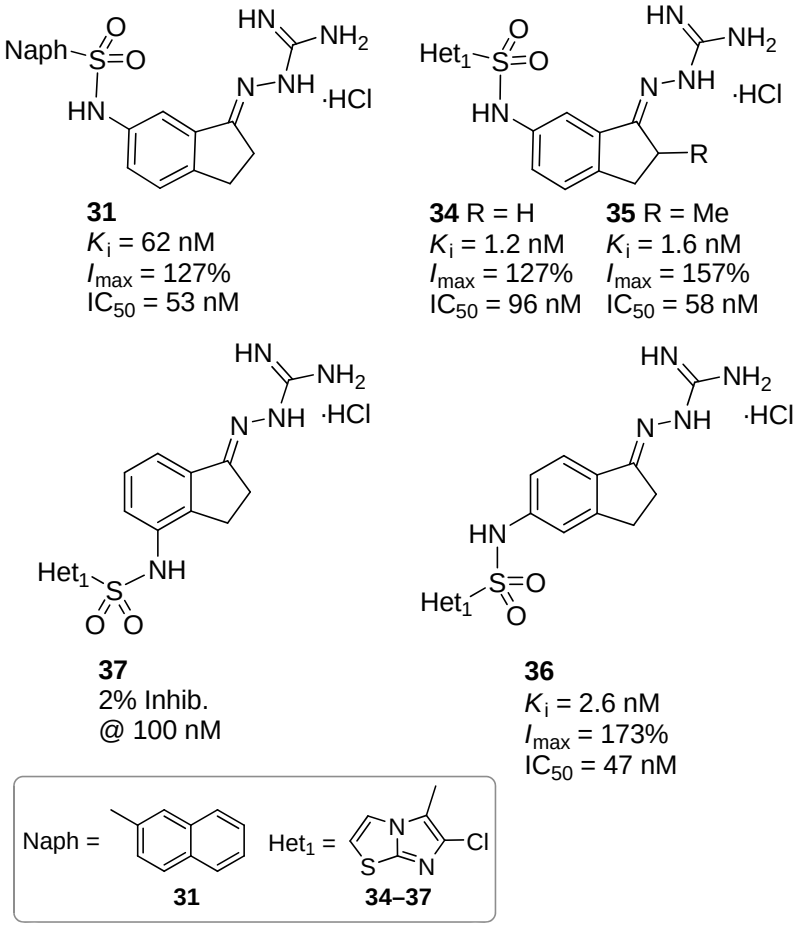
**Scheme S1.** *Reagents and conditions*: (i) Aminoguanidine hydrogencarbonate or 2-hydrazino-4,5-dihydro-1*H*-imidazole hydrobromide, 37% HCl, solvent, reflux.

$Het_1$ = 6-chloroimidazo[2,1-*b*]thiazol-5-yl.



**(*E*)-35**

**Figure S1.** Key NMR responses for compound **35**: 1D NOESY experiments**.**




**31**
$K_i$ = 62 nM
$I_{max}$ = 127%
$IC_{50}$ = 53 nM

**34** R = H
$K_i$ = 1.2 nM
$I_{max}$ = 127%
$IC_{50}$ = 96 nM

**35** R = Me
$K_i$ = 1.6 nM
$I_{max}$ = 157%
$IC_{50}$ = 58 nM

**37**
2% Inhib.
@ 100 nM

**36**
$K_i$ = 2.6 nM
$I_{max}$ = 173%
$IC_{50}$ = 47 nM

Naph = **31**

$Het_1$ = **34–37**

**Figure S2**

**Table S1.** Selectivity over several receptors and serotonin transporter (SERT) of compounds **31**, **32**, **34**–**36** and **38**–**40**.[a]

| Cpd. | Ar(Het) | $\alpha_1$[b] | $\alpha_2$[c] | 5-$HT_{1A}$[d] | 5-$HT_{2c}$[d] | SERT[e] |
|---|---|---|---|---|---|---|
| **31** | $Ar_1$ | | $>10^3$ | $>10^3$ | | |
| **32** | $Ar_2$ | | | $>10^3$ | | |
| **34** | $Het_1$ | $>10^3$ | $>10^4$ | $>10^4$ | $>10^4$ | $>10^4$ |
| **35** | $Het_1$ | $>10^3$ | $>10^3$ | $>10^3$ | $>10^3$ | $>10^3$ |
| **36** | $Het_1$ | | $>10^3$ | $>10^4$ | | |
| **38** | $Het_1$ | | $>10^4$ | $>10^3$ | $>10^3$ | $>10^4$ |
| **39** | $Het_1$ | | $>10^3$ | $>10^3$ | | |
| **40** | $Het_1$ | $>10^3$ | $>10^4$ | | $>10^4$ | $>10^4$ |

[a]$IC_{50}$ (nM). [b]Rat $\alpha_1$-adrenoreceptor. [c]Human $\alpha_2$-adrenoreceptor. [d]Human receptor. [e]Human transporter.

## FULL EXPERIMENTAL SECTION

### General Methods

The reaction yields have not been optimized. All reagents obtained from commercial sources were used without further purification. Melting point: *Gallenkamp Melting Point Apparatus* MPD350.BM2.5 with digital thermometer and are uncorrected. IR (KBr disk or thin film): Nicolet 205 FT or Perkin Elmer 1430 spectrophotometers. $^{1}$H NMR: Varian Gemini 300 (300 MHz) and Mercury 400 (400 MHz) spectrometers at 298 °K. Chemical shifts were referenced and expressed in ppm (δ) relative to the central peak of DMSO-$d_6$ (2.49 ppm) and TMS for chloroform-*d*. $^{13}$C NMR: Varian Gemini 300 (75.4 MHz) and Mercury 400 (100.6 MHz) spectrometers at 298 °K. Chemical shifts were referenced and expressed in ppm (δ) relative to the central peak of DMSO-$d_6$ (39.7 ppm) and chloroform-*d* (77.0 ppm). 1D double pulsed field gradient spin-echo NOESY: Bruker DMX-500 (500 MHz). MS were obtained using EI at 70 eV in a Hewlett-Packard spectrometer (HP-5989A model). ESI-HRMS: Mass spectra were obtained using an Agilent LC/MSD-TOF spectrometer. For targeted compounds, the chemical purity was determined by HPLC using the following conditions: Waters Alliance 2690 and 2695 (software Millenium 3.20) and Agilent 1100 (software Chemstation A.06.03) equipment with XBridge C18, 3.5 μ, 0.46x10 cm column; acetonitrile (ACN) / 10 mM ammonium bicarbonate mobile phase, gradient conditions: 0 – 12 min: from 5% ACN until 95% ACN, 12 – 17 min: isocratic 95% ACN; flow rate 1 ml/min; temperature 35ºC; λ = 210 nm; $t_R$ = 5.4 min. All final compounds were >95% purity. TLC: Merck precoated silica gel 60 F254 plates using UV light (254 nm) as a visualizing agent and/or $H_2PtCl_2$ 3% aq. / KI 10% aq. (1:1) or $KMnO_4$ ethanolic solution. Column chromatography was performed on silica gel 60 ACC 35-70 μm Chromagel (SDS).

### Materials

5-Aminoindan-1-ona **23,** 4-aminoindan-1-one **25,** 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride, 4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-7-sulfonyl chloride, aminoguanidine hydrogencarbonate and 2-hydrazino-4,5-dihydro-1*H*-imidazole hydrobromide are commercial. 6-Aminoindan-1-one **17**[11], *N*-(3-oxo-2,3-dihydro-1*H*-inden-5-yl)naphthalene-2-sulfonamide **18**[11], 6-amino-2-methylindan-1-one **20**[11], 3,3-dimethyl-6-nitroindan-1-one **27**[12] were prepared as previously described.

### Synthesis of indanone sulfonamides 19, 21, 22, 24, 26, 29 and 30. General procedure

To a stirred solution of aminoindanones **17**, **20**, **23** or **25** (1.0 equiv) in dry pyridine was added dropwise a solution of the corresponding sulfonyl chloride (1.0 equiv) in dry pyridine under argon atmosphere. The resulting mixture was stirred at room temperature for 6.5 h. The reaction mixture

was evaporated to dryness. The residue obtained was purified by silica gel column chromatography ($CH_2Cl_2$:MeOH mixtures of increasing polarity as eluent).

**4-methyl-*N*-(3-oxo-2,3-dihydro-1*H*-inden-5-yl)-3,4-dihydro-2*H*-1,4-benzoxazine-7-sulfonamide 19**

The above procedure was followed using 6-aminoindan-1-one **17** (0.12 g, 0.81 mmol) and 4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-7-sulfonyl chloride (0.20 g, 0.81 mmol) in dry pyridine (4 mL). Indanone sulfonamide **19** (0.25 g, 84%) was obtained as a yellow solid.

Mp 189−90 °C. IR (KBr disk): ν(NH) 3242; ν(C=O) 1707; ν($SO_2$) 1327, 1155 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.66−2.70 (m, 2H), 2.85 (s, 3H), 3.08 (t, *J* = 5.5Hz, 2H), 3.25−3.28 (m, 2H), 4.28−4.30 (m, 2H), 6.70 (d, *J* = 8.7 Hz, 1H), 7.02−7.05 (m, 2H), 7.34−7.40 (m, 2H), 7.53 (dd, *J* = 2.1, 8.4 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): δ 25.1 ($CH_2$), 36.5 ($CH_2$), 38.1 ($CH_3$), 47.9 ($CH_2$), 64.8 ($CH_2$), 110.3 (CH), 114.7 (CH), 115.4 (CH), 117.3 (CH), 127.2 (CH), 127.9 (CH); 130.9, 136.5, 137.2, 137.3, 147.6, 151.3, 207.6 (C=O) ppm. EI-MS *m/z* (%): 358 (65) [$M^{+\bullet}$], 343 (13) [$M^{+\bullet}$–15], 148 (100) [$M^{+\bullet}$–210].

**6-Chloro-*N*-(3-oxo-2,3-dihydro-1*H*-inden-5-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 21**

The above procedure was followed using 6-aminoindan-1-one **17** (0.30 g, 2.40 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.524 g, 2.40 mmol) in dry pyridine (10 mL). Indanone sulfonamide **21** (0.532 g, 53%) was obtained as a yellow foamy solid.

Mp 69–70 °C. IR (KBr disk): ν(NH) 3117; ν(C=O) 1717; ν($SO_2$) 1236, 1115 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.67−2.71 (m, 2H), 3.08 (t, *J* = 5.8 Hz, 2H), 7.04 (d, *J* = 4.2 Hz, 1H), 7.4 (dd, *J* = 0.9, 8.7 Hz, 1H), 7.47−7.50 (m, 2H), 7.87 (d, *J* = 4.2 Hz, 1H), 8.07 (br s, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): δ 25.4 ($CH_2$), 36.7 ($CH_2$), 114.7 (CH), 116.3 (CH), 117.9, 120.2 (CH), 127.8 (CH), 128.5 (CH), 135.0, 138.0, 138.1, 150.1, 152.8, 206.3 (C=O) ppm. ESI-HRMS calc. for $C_{14}H_{10}N_3O_3S_2Cl$ $[M+H]^+$: 367.9924; found: 367.9936.

**6-Chloro-*N*-(2-methyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 22**

The above procedure was followed using 6-aminoindan-2-methylindan-1-one **20** (0.50 g, 3.10 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.797 g, 3.10 mmol) in dry pyridine (20 mL). Indanone sulfonamide **22** (1.59 g, 67%) was obtained as an off-white foamy solid.

Mp 69–70 °C. IR (KBr disk): ν(NH) 3119; ν(C=O) 1702; ν($SO_2$) 1250, 1141 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.28 (d, *J* = 7.2 Hz, 3H), 2.62−2.75 (m, 2H), 3.29−3.37 (m, 1H), 7.04 (d, *J* = 4.5 Hz, 1H), 7.37 (dd, *J* = 1.5, 8.2 Hz, 1H), 7.47−7.50 (m, 2H), 7.87 (d, *J* = 4.5 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): δ 16.1 ($CH_3$), 34.5 ($CH_2$), 42.6 (CH), 114.7 (CH), 116.5 (CH), 120.2 (CH),

127.7 (CH), 128.5 (CH), 135.1, 137.4, 138.0, 150.1, 151.1, 208.8 (C=O) ppm. EI-MS *m/z* (%): 381 (1) [$M^{+\bullet}$], 317 (64) [$M^{+\bullet}$–64], 282 (100) [$M^{+\bullet}$–99].

**6-Chloro-*N*-(1-oxo-2,3-dihydro-1*H*-inden-5-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 24**

The above procedure was followed using 5-aminoindan-1-one **23** (0.35 g, 2.76 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.71 g, 2.76 mmol) in dry pyridine (10 mL). Indanone sulfonamide **24** (0.49 g, 23%) was obtained as a yellow solid.

Mp 212−3 °C. IR (KBr disk): ν(NH) 3113; ν(C=O) 1675; ν($SO_2$) 1241, 1145 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.63−2.67 (m, 2H), 3.03−3.05 (m, 2H), 7.07 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.12 (d, *J* = 4.5 Hz, 1H), 7.28 (d, *J* = 1.2 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 4.5 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): δ 25.7 ($CH_2$), 36.2 ($CH_2$), 114.8 (CH), 115.7 (CH), 118.5 (CH), 120.0 (CH), 125.1 (CH), 125.7, 133.0, 142.6, 157.2, 206.1 (C=O) ppm. EI-MS *m/z* (%): 367 (5) [$M^{+\bullet}$], 303 (47) [$M^{+\bullet}$–64], 267 (100) [$M^{+\bullet}$–100].

**6-Chloro-*N*-(1-oxo-2,3-dihydro-1*H*-inden-4-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 26**

The above procedure was followed using 4-aminoindan-1-one **25** (0.50 g, 3.40 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.87 g, 3.40 mmol) in dry pyridine (15 mL). Indanone sulfonamide **26** (0.572 g, 45%) was obtained as a yellow solid.

Mp 211−2 °C. IR (KBr disk): ν(NH) 3115; ν(C=O) 1687; ν($SO_2$) 1245, 1143 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.67 (t, *J* = 5.7 Hz, 2H), 3.04 (t, *J* = 5.8 Hz, 2H), 4.45 (br s, 1H), 7.19 (d, *J* = 4.2 Hz, 1H), 7.30−7.35 (m, 1H), 7.46−7.50 (m, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 3.9 Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): δ 23.0 ($CH_2$), 35.6 ($CH_2$), 114.6 (CH), 118.7, 119.8 (CH), 121.5 (CH), 128.2 (CH), 129.8 (CH), 133.5, 137.2, 138.0, 149.7, 149.8, 207.0 (C=O) ppm. ESI-HRMS calc. for $C_{14}H_{10}N_3O_3S_2Cl$ $[M+H]^+$: 367.9924; found: 367.9920.

**6-Amino-3,3-dimethylindan-1-one 28**

To a stirred solution of 3,3-dimethyl-6-nitroindan-1-one **27** (3.4 g, 16.47 mmol) in a 50% acetic acid aqueous solution (64 mL) at 90 °C was added iron (7.9 g, 141.4 mmol) in portions. The resulting suspension was stirred at the same temperature for 45 min. The reaction mixture was filtered through Celite and evaporated to dryness. The resultant residue was dissolved in $CH_2Cl_2$ and washed with saturated $NaHCO_3$ aqueous solution (3 × 100 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The residue obtained was purified by silica gel column chromatography ($CH_2Cl_2$: MeOH mixtures of increasing polarity as eluent) to afford 6-amino-3,3-dimethylindan-1-one **28** (1.85 g, 64%) as a brown solid.

Mp 67−8 °C. IR (KBr): ν($NH_2$) 3467, 3419; ν(C=O) 1682 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 6H), 2.56 (s, 2H), 3.73 (br s, 2H), 6.92−6.93 (m, 1H), 6.97 (dd, *J*= 2.4, 7.8 Hz, 1H), 7.27−7.29 (m, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 75.4 Hz): δ 30.1 ($CH_3$), 37.8, 53.5 ($CH_2$), 107.2 (CH),

123.0 (CH), 124.1 (CH), 136.4, 146.0, 154.6, 206.1 (C=O) ppm. EI-MS m/z (%): 175 (80) [$M^{+\bullet}$], 160 (100) [$M^{+\bullet}$–15].

**6-Chloro-*N*-(1,1-dimethyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl)imidazo[2,1-b][1,3]thiazole-5-sulfonamide 29**

The above procedure was followed using 6-amino-3,3-dimethylindan-1-one **28** (0.50 g, 2.85 mmol) and 6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride (0.74 g, 2.85 mmol) in dry pyridine (10 mL). Indanone sulfonamide **29** (0.81 g, 72%) was obtained as a yellow foamy solid.

Mp 195−6 °C. IR (KBr disk): ν(NH) 3241; ν(C=O) 1702; ν($SO_2$) 1250, 1181 $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 1.47 (s, 6H), 2.67 (s, 2H), 7.19 (d, *J* = 4.8 Hz, 1H), 7.43 (d, *J* = 1.5 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.64 (dd, *J* = 2.2, 9.0 Hz, 1H), 8.01 (d, *J* = 4.2 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 75.4 MHz): δ 29.7 ($CH_3$), 38.3 ($CH_2$), 53.0, 114.5 (CH), 114.7 (CH), 118.3, 120.1 (CH), 124.6 (CH), 128.1 (CH), 135.8, 137.8, 149.8, 160.8, 206.0 (C=O) ppm. EI-MS *m/z* (%): 395 (0.5) [$M^{+\bullet}$], 331 (60) [$M^{+\bullet}$–64], 316 (48) [$M^{+\bullet}$–79], 295 (100) [$M^{+\bullet}$–100].

**6-Chloro-*N*-methyl-*N*-(3-oxo-2,3-dihydro-1*H*-inden-5-yl)imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide 30**

To a stirred solution of indanone sulfonamide **21** (0.50 g, 1.36 mmol) in dry DMF (15 mL) was added $K_2CO_3$ (1.13 g, 8.16 mmol) under argon atmosphere at room temperature. After stirring for 3 h, MeI (0.13 mL, 2.04 mmol) was added. The reaction solution was allowed to stir overnight at the same temperature and was evaporated to dryness. Water (150 mL) was added to the crude reaction and was extracted with EtOAc (3 × 100 mL). The organic extracts was dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The resulting residue was purified by silica gel column chromatography ($CH_2Cl_2$:MeOH as eluent). Indanone sulfonamide **30** (0.42 g, 81%) was obtained as a white solid.

Mp 198−9 °C. IR (KBr disk): ν(NH) 3117; ν(C=O) 1713; ν($SO_2$) 1248, 1180 $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 2.72−2.75 (m, 2H), 3.15 (t, *J* = 5.9 Hz, 2H), 3.37 (s, 3H), 6.92 (d, *J* = 4.8 Hz, 1H), 7.32 (t, *J* = 2.4 Hz, 1H), 7.46−7.49 (m, 2H), 7.56 (dd, *J* = 2.1, 9.0 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 75.4 MHz): δ 25.5 ($CH_2$), 36.5 ($CH_2$), 38.3 ($CH_3$), 114.3 (CH), 116.9, 119.9 (CH), 120.7 (CH), 127.4 (CH), 133.7 (CH), 137.7, 138.7, 140.0, 150.1, 154.7, 206.0 (C=O) ppm.

**Synthesis of Indanylsulfonamide guanylhydrazones 31–41. General procedure**

To a solution of indanone sulfonamides **18**, **19**, **21**, **22**, **24**, **26**, **29** and **30** (1.0 equiv) in the suitable solvent was added a suspension of aminoguanidine hydrogencarbonate or 2-hydrazino-4,5-dihydro-1*H*-imidazole hydrobromide (1.1 equiv) in an excess of hydrochloric acid and the mixture was heated to reflux for 18h. The reaction mixture was cooled in an ice bath to obtain a solid that was

isolated by filtration or the crude reaction was evaporated to dryness and was purified by crushing with a suitable solvent.

**2-{6-[(2-Naphthylsulfonyl)amino]-2,3-dihydro-1*H*-inden-1-ylidene}hydrazinecarboximidamide hydrochloride 31**

The above procedure was followed using aminoguanidine hydrogencarbonate (45.0 mg, 0.33 mmol) in 1N HCl aqueous solution (2 mL) and indanone sulfonamide **18** (0.10 g, 0.30 mmol) in MeOH/MeCN solution (1:1, 10 mL). The residue was crushed with MeCN to afford the hydrochloride **31** (35.6 mg, 36%) as a white solid.

Mp 256−7°C. IR (KBr disk): ν($NH_2$) 3148; ν(NH) 3050; ν(C=NH) 1675; ν($SO_2$) 1333, 1153 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.94−2.96 (m, 2H), 3.10−3.13 (m, 2H), 7.22 (d, $J$ = 8.0 Hz, 1H), 7.37 (d, $J$ = 8.0 Hz, 1H), 7.78−7.96 (m, 7H ArH + guanyl), 7.94 (d, $J$ = 8.0 Hz, 1H) 8.16 (d, $J$ = 8.0 Hz, 1H), 8.23−8.29 (m, 2H), 8.67 (s, 1H), 10.67 (br s, 1H, $NHSO_2$), 10.87 (br s, 1H, NH) ppm. $^{13}C$ NMR (DMSO-$d_6$, 75.4 MHz): δ 27.4 ($CH_2$), 28.2 ($CH_2$), 114.2 (CH), 122.0 (CH), 124.3 (CH), 126.2 (CH), 127.6 (CH), 127.8 (CH), 128.1 (CH), 128.9 (CH), 129.1 (CH), 129.3 (CH), 131.5, 134.2, 136.3, 136.6, 137.5, 145.2, 155.6 (C=N), 160.8 (C=N) ppm. ESI-HRMS calc. for $C_{20}H_{19}N_5O_2S$ $[M+H]^+$: 394.1337; found: 394.1332.

**2-(6-{[(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-7-yl)sulfonyl]amino}- 2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 32**

The above procedure was followed using aminoguanidine hydrogencarbonate (42.0 mg, 0.31 mmol) in 37% HCl aqueous solution (2 mL) and indanone sulfonamide **19** (0.10 g, 0.28 mmol) in absolute EtOH (4 mL). The residue was crushed with $Et_2O$ to afford the hydrochloride **32** (80.0 mg, 63%) as a white solid.

Mp 190−1 °C. IR (KBr disk): ν($NH_2$) 3363; ν(NH) 3164; ν(C=NH) 1674; ν($SO_2$) 1319, 1152 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.80 (s, 3H), 2.83−2.85 (m, 2H), 2.97−2.99 (m, 2H), 3.24 (t, $J$ = 4.1 Hz, 2H), 4.22−4.25 (m, 2H), 6.72 (d, $J$ = 8.4 Hz, 1H), 6.96 (dd, $J$ = 1.9, 8.2 Hz, 1H), 7.07 (dd, $J$ = 2.2, 8.8 Hz, 2H), 7.24 (d, $J$ = 7.8 Hz, 1H), 7.64 (d, $J$ = 1.8 Hz, 1H), 7.77 (br s, 3H, guanyl), 10.11 (br s, 1H, $NHSO_2$), 11.12 (br s, 1H, NH) ppm. $^{13}C$ NMR (DMSO-$d_6$, 75.4 MHz): δ 27.4 ($CH_2$), 28.6 ($CH_2$), 38.0 ($CH_3$), 47.4 ($CH_2$), 64.7 ($CH_2$), 110.2 (CH), 113.6 (CH), 115.1 (CH), 116.6 (CH), 124.0 (CH), 126.1 (CH), 131.7, 136.6, 137.2, 137.4, 144.8, 147.0, 155.8 (C=N), 160.9 (C=N) ppm. ESI-HRMS calc. for $C_{19}H_{22}N_6O_3S$ $[M+H]^+$: 415.1545; found: 415.1546.

***N*-[3-(4,5-dihydro-1*H*-imidazol-2-ylhydrazono-2,3-dihydro-1*H*-inden-5-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-7-sulfonamide hydrohalide 33**

The above procedure was followed using 2- hydrazino-4,5-dihydro-1*H*-imidazole hydrohydrobromide (83.3 mg, 0.55 mmol) in 37% HCl aqueous solution (2 mL) and indanone

sulfonamide **19** (0.15 g, 0.42 mmol) in 50% EtOH aqueous solution (10 mL). The hydrohalide **33** was obtained as a white solid (0.14 g, 70%).

Mp 264−5 °C. IR (KBr disk): ν($NH_2$) 3346; ν(NH) 3024; ν($NCH_3$) 2870; ν(C=NH) 1665; ν($SO_2$) 1320, 1149 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.81−2.83 (m, 5H), 2.97−3.01 (m, 2H), 3.22−3.25 (m, 2H), 3.72 (s, 4H), 4.23 (t, $J$ = 4.2 Hz, 2H), 6.72 (d, $J$ = 8.4 Hz, 1H), 6.96 (dd, $J$ = 2.1, 8.4 Hz, 1H), 7.08 (dd, $J$ = 2.0, 8.2 Hz, 2H), 7.25 (d, $J$ = 8.4 Hz, 1H), 7.62 (d, $J$ = 2.1 Hz, 1H), 8.47 (br s, 1H, NH), 10.17 (br s, 1H, $NHSO_2$), 11.66 (br s, 1H, NH) ppm. $^{13}C$ NMR (DMSO-$d_6$, 75.4 MHz): δ 27.4 ($CH_2$), 28.6 ($CH_2$), 33.7 ($CH_2$), 38.0 ($CH_3$), 42.8 ($CH_2$), 47.4 ($CH_2$), 64.7 ($CH_2$), 110.2 (CH), 113.2 (CH), 115.1 (CH), 116.5 (CH), 124.0 (CH), 126.2 (CH), 131.6, 136.6, 137.2, 144.8, 147.0, 158.2 (C=N), 162.3 (C=N) ppm. ESI-HRMS calc. for $C_{21}H_{24}N_6O_3S$ $[M+H]^+$: 441.1705; found: 441.1703.

**2-(6-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 34**

The above procedure was followed using aminoguanidine hydrogencarbonate (102.0 mg, 0.75 mmol) in 37% HCl aqueous solution (5 mL) and indanone sulfonamide **21** (0.25 g, 0.68 mmol) in absolute EtOH (10 mL). The hydrochloride salt **34** (0.185 g, 59%) was obtained as a white solid.

Mp 219−20 °C. IR (KBr disk): ν($NH_2$) 3432; ν(NH) 3116; ν(C=NH) 1673; ν($SO_2$) 1355, 1148 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 2.82 (t, $J$ = 6.3 Hz, 2H), 3.00−3.02 (m, 2H), 7.05 (dd, $J$ = 2.1, 8.1 Hz, 1H), 7.29 (d, $J$ = 8.1 Hz, 1H), 7.59−7.61 (m, 2H), 7.67 (br s, 3H, guanyl), 8.06 (d, $J$ = 4.5 Hz, 1H), 10.93 (br s, 1H, $NHSO_2$), 10.99 (br s, 1H, NH) ppm. $^{13}C$ NMR (DMSO-$d_6$, 100.6 MHz): δ 27.5 ($CH_2$), 28.4 ($CH_2$), 114.3 (CH), 116.9 (CH), 117.7, 120.2 (CH), 124.4 (CH), 126.5 (CH), 135.5, 136.7, 137.7, 145.9, 149.8, 155.8 (C=N), 160.6 (C=N) ppm. ESI-HRMS calc. for $C_{15}H_{14}N_7O_2S_2Cl$ $[M+H]^+$: 424.0412; found: 424.0409.

**2-(6-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2-methyl-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 35**

The above procedure was followed using aminoguanidine hydrogencarbonate (59.0 mg, 0.43 mmol) in 2.5 N HCl aqueous solution (5 mL) and indanone sulfonamide **22** (150.0 mg, 0.39 mmol) in MeCN (10 mL). The hydrochloride salt **35** (0.175 g, 95%) was obtained as a white solid.

Mp >300 °C. IR (KBr disk): ν($NH_2$) 3425; ν(NH) 3150; ν(C=NH) 1678; ν($SO_2$) 1354, 1151 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 1.10 (d, $J$ = 7.1 Hz, 3H), 3.22−3.27 (m, 1H), 3.40−3.45 (m, 2H), 7.02 (dd, $J$ = 2.0, 8.5 Hz, 1H), 7.26 (d, $J$ = 8.1 Hz, 1H), 7.58−7.60 (m, 2H), 7.69 (br s, 3H, guanyl), 8.00 (d, $J$ = 4.5 Hz, 1H), 10.91 (br s, 1H, $NHSO_2$), 11.10 (br s, 1H, NH) ppm. $^{13}C$ NMR (DMSO-$d_6$, 100.6 MHz): δ 17.5 ($CH_3$), 34.4 (CH), 37.0 ($CH_2$), 115.2 (CH), 166.7 (CH), 117.7, 120.1 (CH), 124.8 (CH), 126.6 (CH), 135.4, 136.4, 136.6, 144.0, 149.6, 155.8 (C=N), 163.3 (C=N) ppm. ESI-HRMS calc. for $C_{16}H_{16}N_7O_2S_2Cl$ $[M+H]^+$: 438.0567; found: 438.0568.

**2-(5-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 36**

The above procedure was followed using aminoguanidine hydrogencarbonate (101.8 mg, 0.75 mmol) in 37% HCl aqueous solution (2 mL) and indanone sulfonamide **24** (0.25 g, 0.68 mmol) in 50% EtOH aqueous solution (10 mL). The residue was crushed with i-PrOH (2 mL) to afford the hydrochloride **36** (0.15 g, 30%) as a yellow solid.

Mp 249−50 °C. IR (KBr disk): ν($NH_2$) 3410; ν(NH) 3262; ν(C=NH) 1677; ν($SO_2$) 1356, 1150 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.74−2.78 (m, 2H), 3.00−3.01 (m, 2H), 7.06−7.12 (m, 2H), 7.61 (br s, 3H, guanyl), 7.66−7.73 (m, 2H), 8.07 (d, $J$ = 4.5 Hz, 1H), 10.79 (br s, 1H, $NHSO_2$), 11.32 (br s, 1H, NH) ppm. $^{13}C$ NMR (DMSO-$d_6$, 100.6 MHz): δ 27.9 ($CH_2$), 28.4 ($CH_2$), 116.1 (CH), 117.6 (CH), 118.5 (CH), 120.2 (CH), 123.3 (CH), 133.3, 137.5, 139.6, 150.4, 150.7, 155.8 (C=N), 160.6 (C=N) ppm. ESI-HRMS calc. for $C_{15}H_{14}N_7O_2S_2Cl$ $[M+H]^+$: 424.0412; found: 424.0409.

**2-(4-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 37**

The above procedure was followed using aminoguanidine hydrogencarbonate (53.0 mg, 0.39 mmol) in 2.5 N HCl aqueous solution (2 mL) and indanone sulfonamide **26** (130.0 mg, 0.35 mmol) in MeCN (20 mL). The residue was crushed with MeCN to afford the hydrochloride **37** (0.106 g, 66%) as a white solid.

Mp >300 °C. IR (KBr disk): ν($NH_2$) 3469; ν(NH) 3149; ν(C=NH) 1676; ν($SO_2$) 1398, 1139 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 2.75−2.89 (m, 2H), 2.87−2.88 (m, 2H), 7.10 (d, $J$ = 8.0 Hz, 1H), 7.24−7.29 (m, 1H), 7.62 (d, $J$ = 4.0 Hz, 1H), 7.71 (d, $J$ = 8.0 Hz, 1H), 7.83 (br s, 3H, guanyl), 7.93 (d, $J$ = 4.0 Hz, 1H), 10.71 (br s, 1H, $NHSO_2$), 11.33 (br s, 1H, NH) ppm. $^{13}C$ NMR (DMSO-$d_6$, 100.6 MHz): δ 26.3 ($CH_2$), 27.9 ($CH_2$), 117.0 (CH), 118.2, 120.1 (CH), 120.2 (CH), 126.3 (CH), 128.2 (CH), 132.8, 136.5, 138.7, 143.7, 149.9, 156.1 (C=N), 159.9 (C=N) ppm. ESI-HRMS calc. for $C_{15}H_{14}N_7O_2S_2Cl$ $[M+H]^+$: 424.0412; found: 424.0410.

**2-(6-{[(6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 38**

The above procedure was followed using aminoguanidine hydrogencarbonate (151.3 mg, 1.11 mmol) in 37% HCl aqueous solution (3 mL) and indanone sulfonamide **29** (0.40 g, 1.01 mmol) in absolute EtOH (12 mL). The residue was crushed with i-PrOH to obtain the hydrochloride **38** (0.46 g, 93%) as a white solid.

Mp 225−6 °C. IR (KBr disk): ν($NH_2$) 3367; ν(C=NH) 1677; ν($SO_2$) 1251, 1142 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 1.24 (s, 6H), 2.70 (s, 2H), 7.04 (dd, $J$ = 1.8, 8.1 Hz, 1H), 7.31 (d, $J$ = 8.1 Hz, 1H), 7.55−7.59 (m, 2H), 7.72 (br s, 3H, guanyl), 7.97 (d, $J$ = 4.5 Hz, 1H), 10.98 (br s, 1H, $NHSO_2$), 11.05 (br s, 1H, NH) ppm. $^{13}C$ NMR (DMSO-$d_6$, 75.4 MHz): δ 29.8 ($CH_3$), 33.75 ($CH_3$), 40.93

($CH_2$), 44.45, 114.4 (CH), 116.8 (CH), 117.8 (CH), 120.1, 124.0 (CH), 124.9 (CH), 135.7, 135.9, 136.6, 149.8, 154.3, 155.7 (C=N), 158.2 (C=N) ppm. ESI-HRMS calc. for $C_{17}H_{18}ClN_7O_2S_2$ $[M+H]^+$: 452.0724; found: 452.0726.

**2-(6-{[(6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl](methyl)amino}-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 39**

The above procedure was followed using aminoguanidine hydrogencarbonate (58.8 mg, 0.43 mmol) in 37% HCl aqueous solution (2 mL) and indanone sulfonamide **30** (0.15 g, 0.39 mmol) in absolute EtOH (5 mL). The residue was crushed with i-PrOH to give the hydrochloride **39** (90.0 mg, 49%) as a white solid.

Mp 253−4 °C. IR (KBr disk): ν($NH_2$) 3390; ν(C=NH) 1673; ν($SO_2$) 1350, 1179 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.82−2.86 (m, 2H), 3.09−3.11 (m, 2H), 3.27 (s, 3H), 7.25 (dd, *J*= 2.1, 8.1 Hz, 1H), 7.30 (d, *J* = 4.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 4.2 Hz, 1H), 7.63 (br s, 3H, guanyl), 7.78 (d, *J* = 1.8 Hz, 1H), 10.81 (br s, 1H, NH) ppm. $^{13}C$ NMR (DMSO-$d_6$, 75.4 MHz): δ 28.0 ($CH_2$), 28.2 ($CH_2$), 37.9 ($CH_3$), 115.9, 116.9 (CH), 119.9 (CH), 120.8 (CH), 126.2 (CH), 129.2 (CH), 137.4, 138.1, 139.4, 148.6, 150.6, 155.8 (C=N), 159.5 (C=N) ppm. ESI-HRMS calc. for $C_{16}H_{16}N_7O_2S_2Cl$ $[M+H]^+$: 438.0568; found: 438.0565.

**6-chloro-*N*-[3-(4,5-dihydro-1*H*-imidazol-2-ylhydrazono)-2,3-dihydro-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide hydrohalide 40**

The above procedure was followed using 2-hydrazino-4,5-dihydro-1*H*-imidazole hydrobromide (0.10 g, 0.55 mmol) in 37% HCl aqueous solution (2 mL) and indanone sulfonamide **21** (185.0 mg, 0.50 mmol) in 50% EtOH aqueous solution (10 mL). The hydrohalide **40** (0.10 g, 41%) was obtained as a white solid.

Mp 245−6 °C. IR (KBr disk): ν($NH_2$) 3345; ν(NH) 3125; ν(C=NH) 1667; ν($SO_2$) 1346, 1149 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 2.81−2.85 (m, 2H), 2.98−3.01 (m, 2H), 3.73 (s, 4H), 7.08 (dd, *J* = 2.1, 8.1 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.59−7.62 (m, 2H), 8.11 (d, *J* = 4.5 Hz, 1H), 8.51 (br s, 1H, NH), 11.20 (br s, 1H, $NHSO_2$), 11.61 (br s, 1H, NH) ppm. $^{13}C$ NMR (DMSO-$d_6$, 75.4 MHz): δ 27.5 ($CH_2$), 28.5 ($CH_2$), 33.7 ($CH_2$), 42.9 ($CH_2$), 114.3 (CH), 116.8, 117.7 (CH), 120.3 (CH), 124.6 (CH), 126.5 (CH), 135.5, 136.6, 137.6, 146.0, 149.7, 158.3 (C=N), 162.0 (C=N) ppm. ESI-HRMS calc. for $C_{17}H_{16}N_7O_2S_2Cl$ $[M+H]^+$: 450.0563; found: 450.0568.

**6-Chloro-*N*-[3-(4,5-dihydro-1*H*-imidazol-2-ylhydrazono)-1,1-dimethyl-2,3-dihydro-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide hydrohalide 41**

The above procedure was followed using 2-hydrazino-4,5-dihydro-1*H*-imidazole hydrobromide (0.11 g, 0.55 mmol) in 37% HCl aqueous solution (2 mL) and indanone sulfonamide **29** (0.2 g, 0.50 mmol) in 50% EtOH aqueous solution (10 mL). The residue was crushed with $Et_2O$ to afford the hydrohalide **41** (0.18 g, 69%) as a white solid.

Mp >300 °C. IR (KBr disk): ν($NH_2$) 3255; ν(NH) 3141; ν(C=NH) 1666; ν($SO_2$) 1344, 1179 $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.25 (s, 6H), 2.70 (s, 2H), 3.74 (s, 4H), 7.05 (dd, $J$ = 2.0, 8.4 Hz, 1H), 7.34 (d, $J$ = 8.0 Hz, 1H), 7.55 (d, $J$ = 1.6 Hz, 1H), 7.60 (d, $J$ = 4.4 Hz, 1H), 7.96 (d, $J$ = 4.8 Hz, 1H), 8.30 (br s, 1H, NH), 10.92 (br s, 1H, -NH-$SO_2$-), 11.17 (br s, 1H, NH) ppm. $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz): δ 29.7 ($CH_3$), 40.9, 42.9 ($CH_2$), 44.3 ($CH_2$), 114.5 (CH), 116.9 (CH), 117.8, 120.1 (CH), 124.1 (CH), 125.2 (CH), 135.7, 135.8, 136.5, 149.8, 154.6, 158.1(C=N), 159.8 (C=N) ppm. ESI-HRMS calc. for $C_{19}H_{20}N_7O_2S_2Cl$ $[M+H]^+$: 478.0881; found: 478.0881.

**5-$HT_6$ Binding Assay**

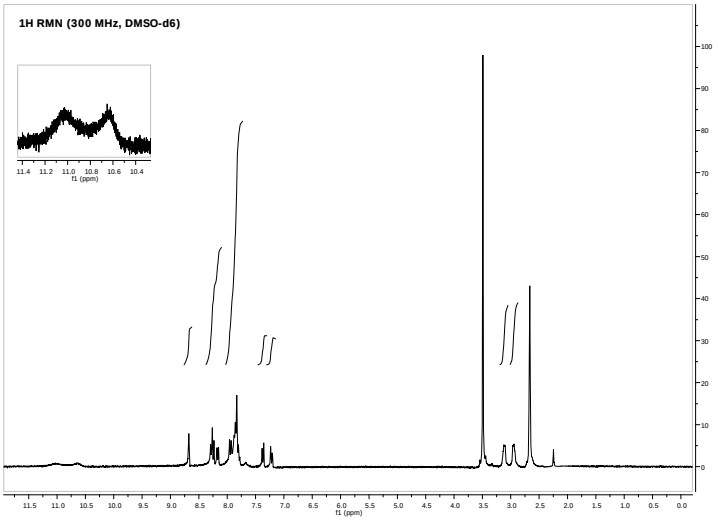
Membranes from HEK-293 with human 5-$HT_6$ receptor expressed were supplied by Receptor Biology. The binding assays were performed as described by Roth et al.[28a] with slight modifications. The radioligand used was [3H]-LSD at 2.7 nM, and the final volume was 200μL. The incubation was initiated by addition of 100 μL of membrane (22.9 μg of protein), and the incubation time was 60 min at 37 °C. After incubation, the membranes were collected onto polyethylenimine-pretreated glass fiber filters (Schleicher & Schnell 3362). The filters were washed with buffer (50 mM Tris Cl, pH = 7.4). Then, filter sections were transferred to vials, and liquid scintillation cocktail was added to each vial. Nonspecific binding was determined with 100 μM serotonin. Competition binding data were analyzed by using the LIGAND program,[28b] and assays were performed in triplicate determinations for each point. A linear regression line of data points is plotted, from which the concentration of competing ligand which displaces 50% of the specific binding of the radioligand ($IC_{50}$ value) is determined and the $K_i$ value is determined based upon the Cheng-Prusof equation: $K_i = IC_{50} / (1 + L/K_D)$ were L is the concentration of free radioligand used in the assay and $K_D$ is the dissociation constant of the radioligand for the receptor.

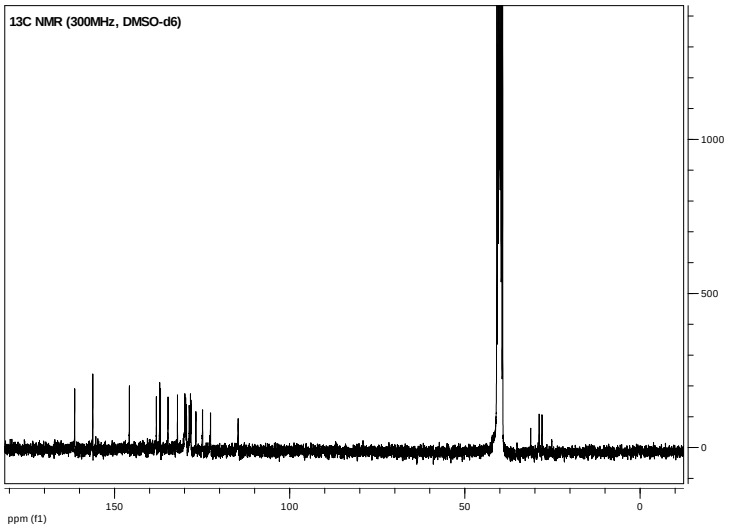
**Adenylyl Cyclase Activity Assay**

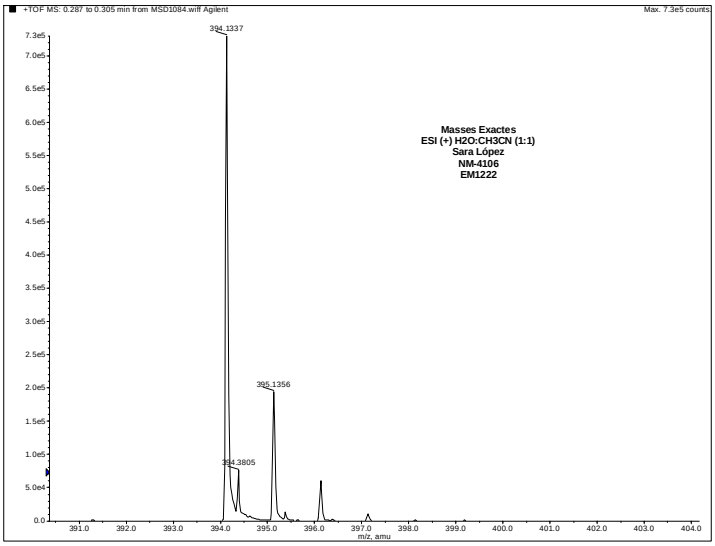
Functional effects of the compounds were evaluated by cAMP measurements on HEK-293F cells stably expressing the human 5-$HT_6$ receptor using a homogeneous time resolved fluorescence (HTRF) assay format. After overnight serum-free medium incubation, cell suspensión (20,000 cells per well) was added in 96-well culture plate in incubation buffer composed of Ham's F12 medium plus 1 mM 3-isobutyl-1-methyl-xanthine (IBMX) and 20 μM pargyline. Forty microliters of cell suspension and 10 μl of either compound or vehicle were added to each well at indicated concentrations for 30 min at 37 °C, in either absence or presence (in antagonist experiments) of 5-HT. The reaction was stopped with 25 μl of cryptate and 25 μl of cross-linked allophycocyanin (XL-665). Plates were incubated for 1 h at room temperature and read at 665 nm/620 nm using a RubyStar Plate reader (BMG LabTech).[29-31]

## NMR SPECTRA AND ESI (+)-HRMS SPECTRA OF TARGETED COMPOUNDS

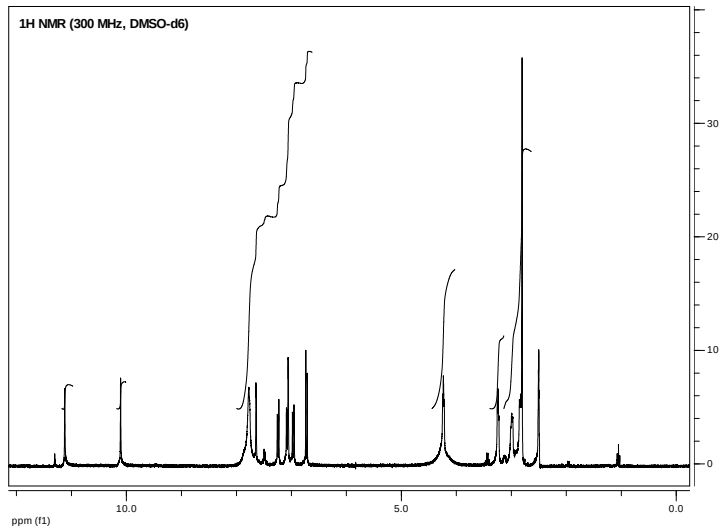
- **2-{6-[(2-Naphthylsulfonyl)amino]-2,3-dihydro-1*H*-inden-1-ylidene}hydrazinecarboximidamide hydrochloride 31**

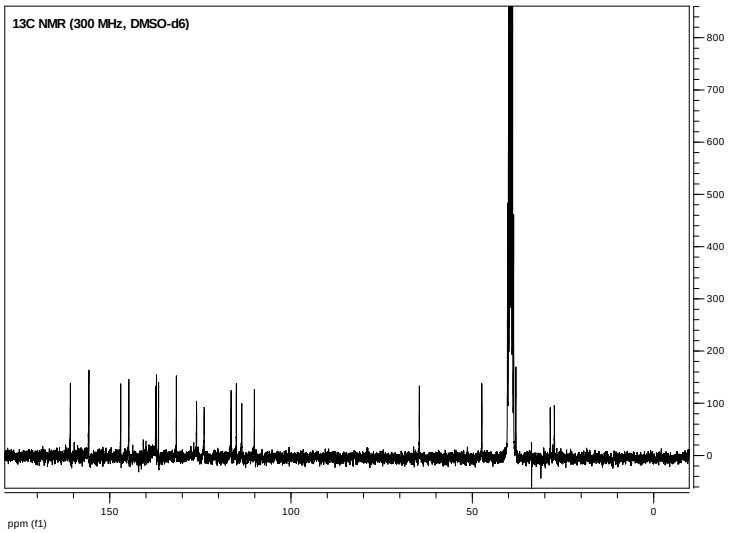


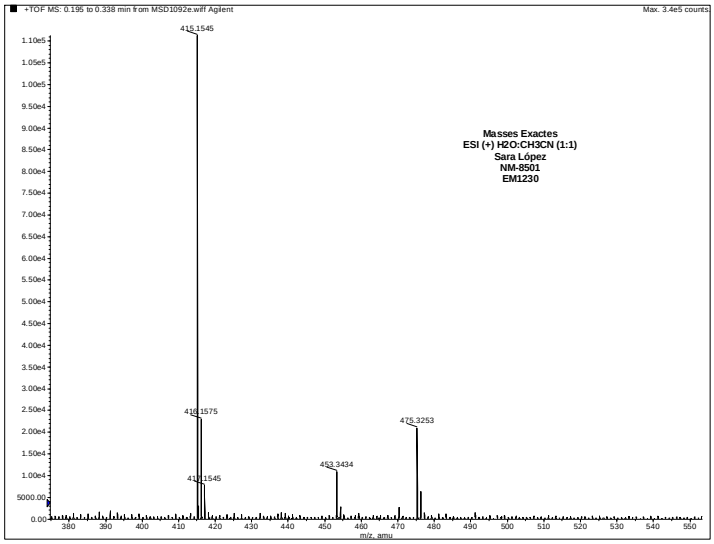



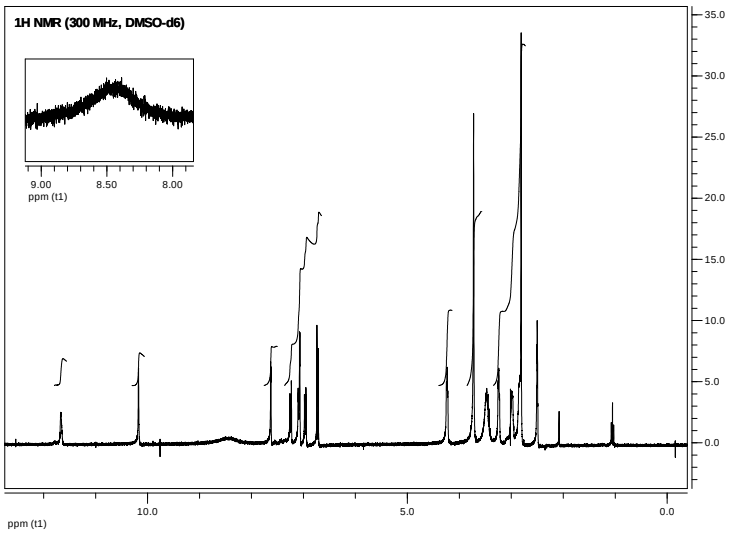
- **2-(6-{[(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-7-yl)sulfonyl]amino}- 2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 32**

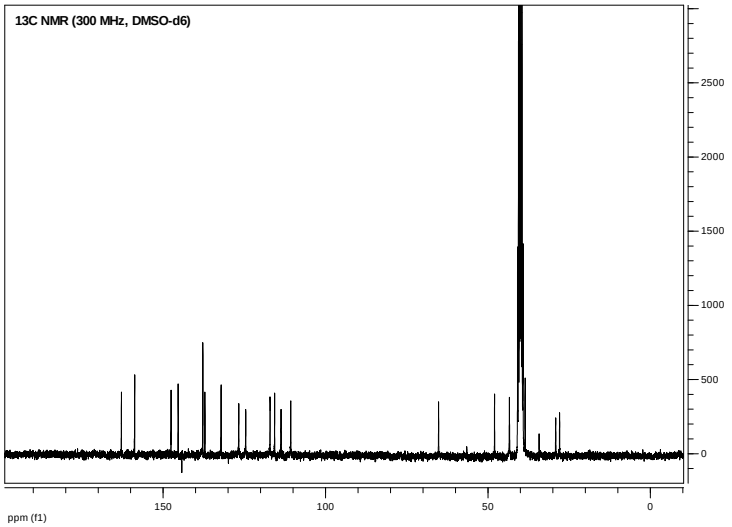


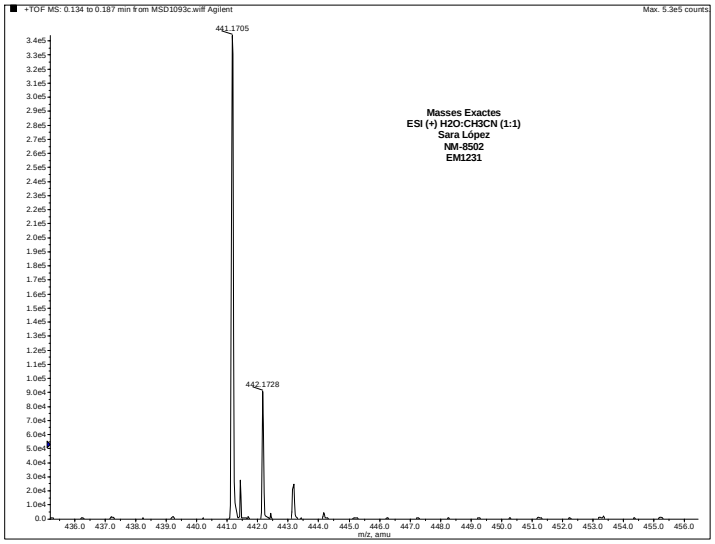



- ***N*-[3-(4,5-dihydro-1*H*-imidazol-2-ylhydrazono-2,3-dihydro-1*H*-inden-5-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-7-sulfonamide hydrohalide 33**

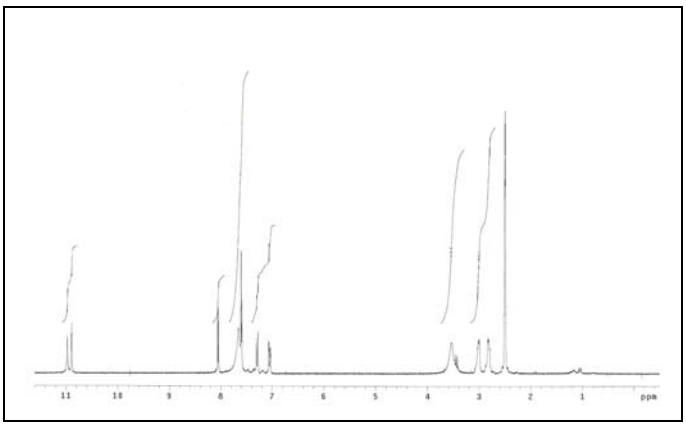


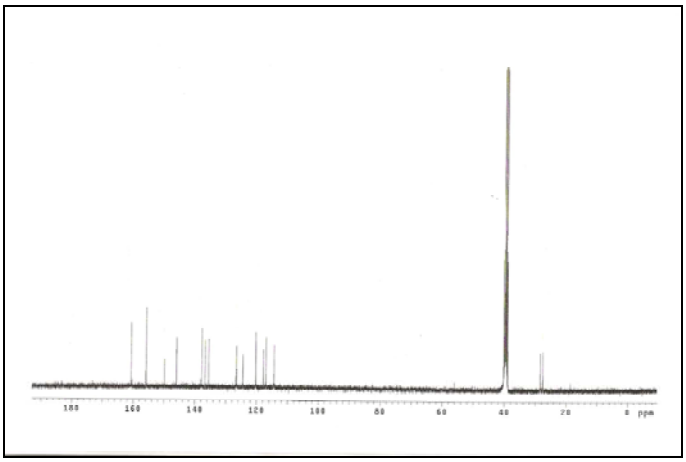



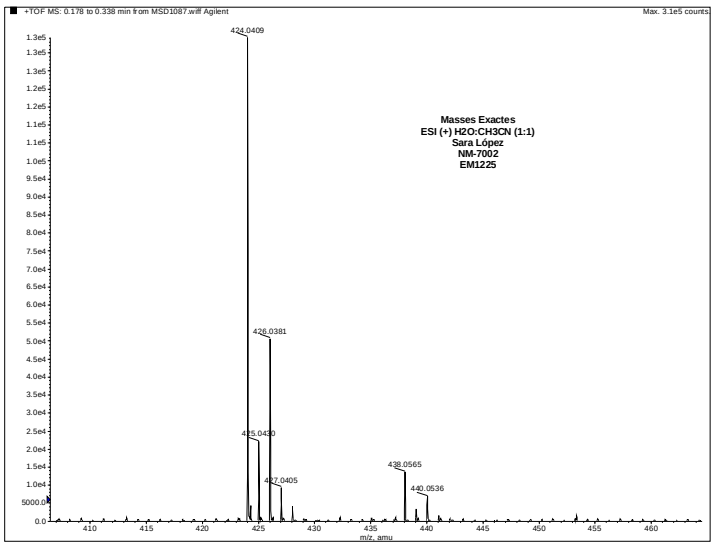
- **2-(6-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 34**

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

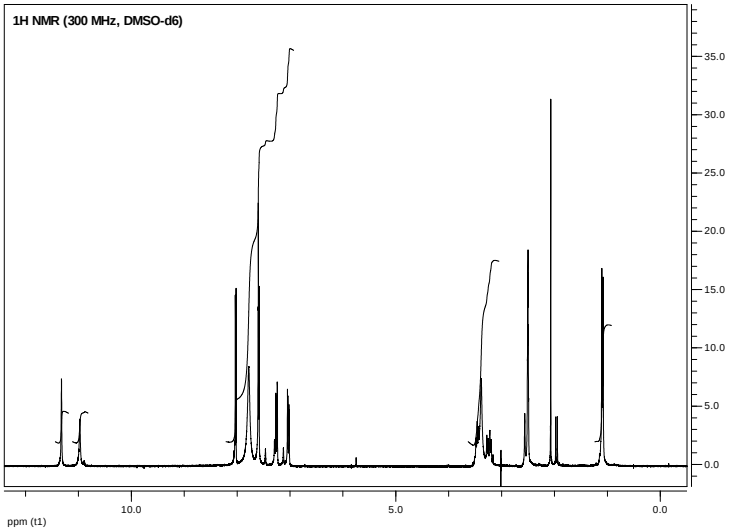


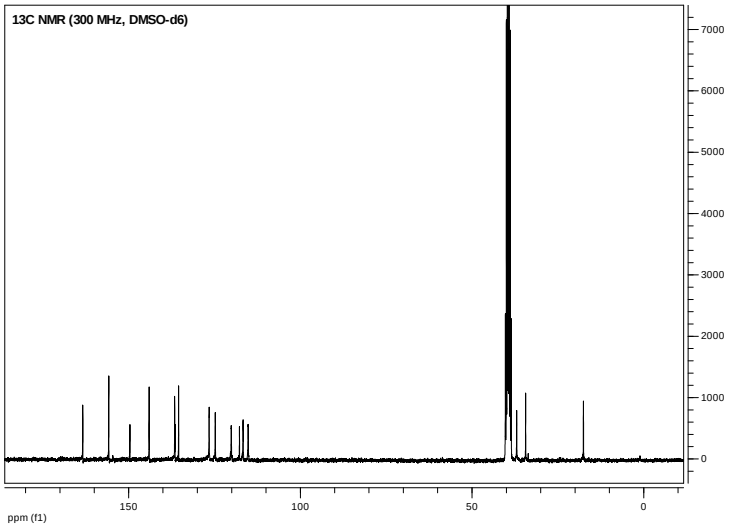
$^{13}$C NMR (100.6 MHz, DMSO-$d_6$)

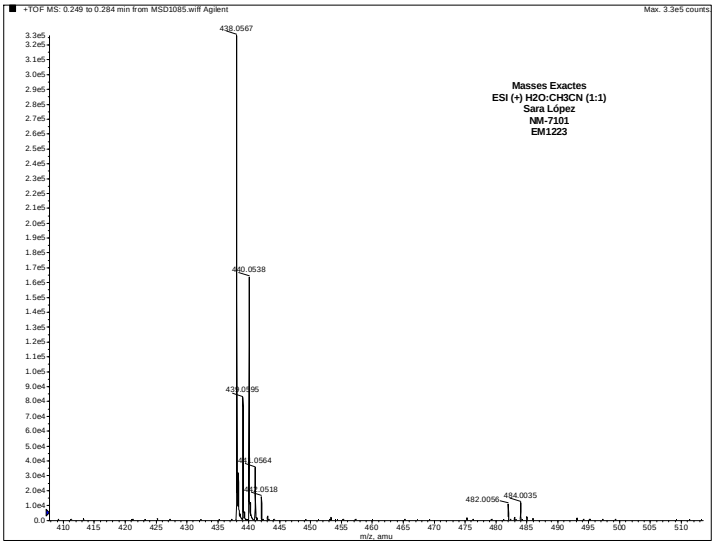




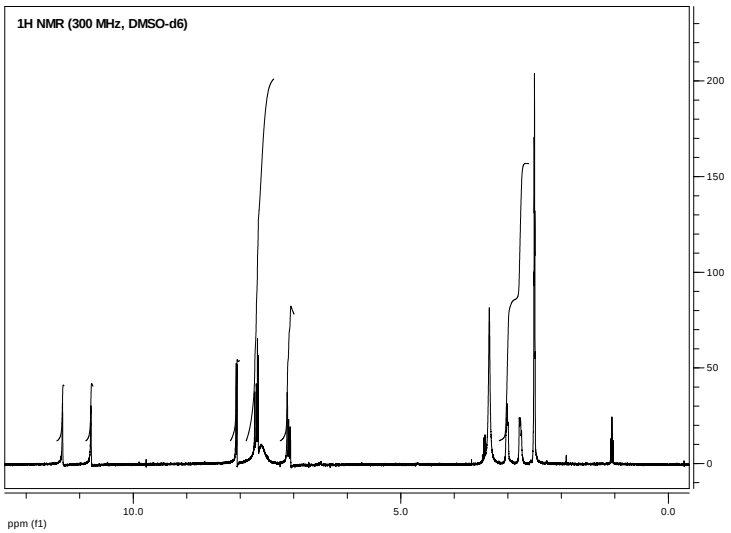
- **2-(6-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2-methyl-2,3-dihydro- 1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 35**

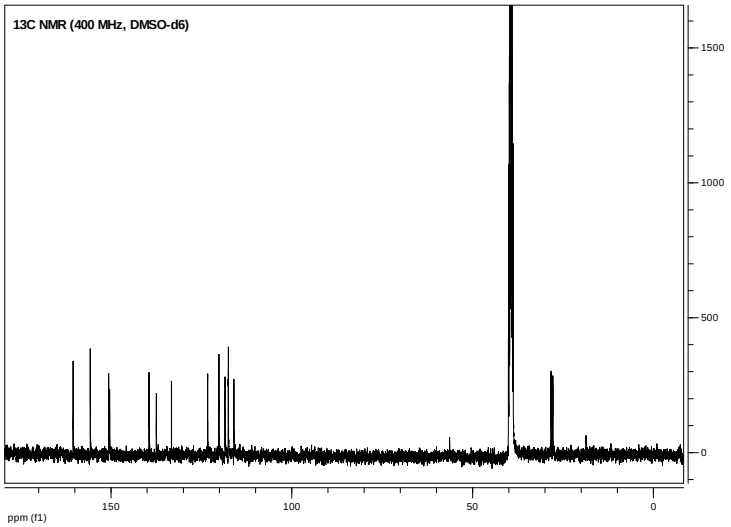


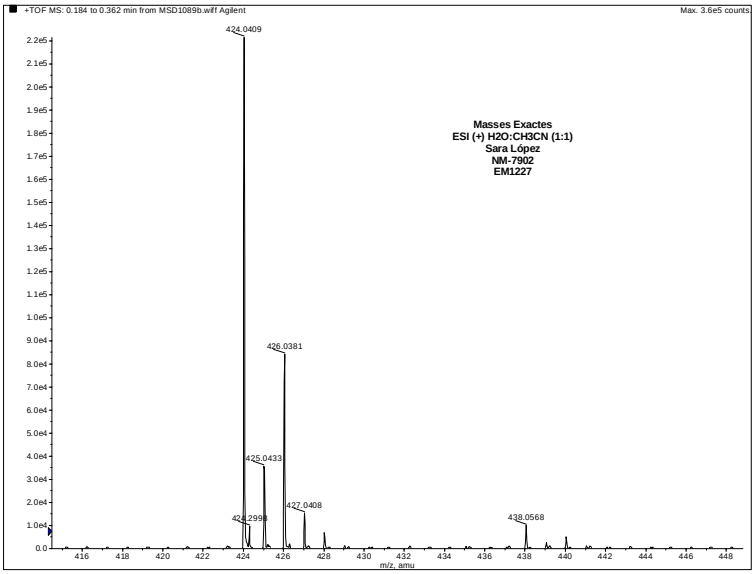



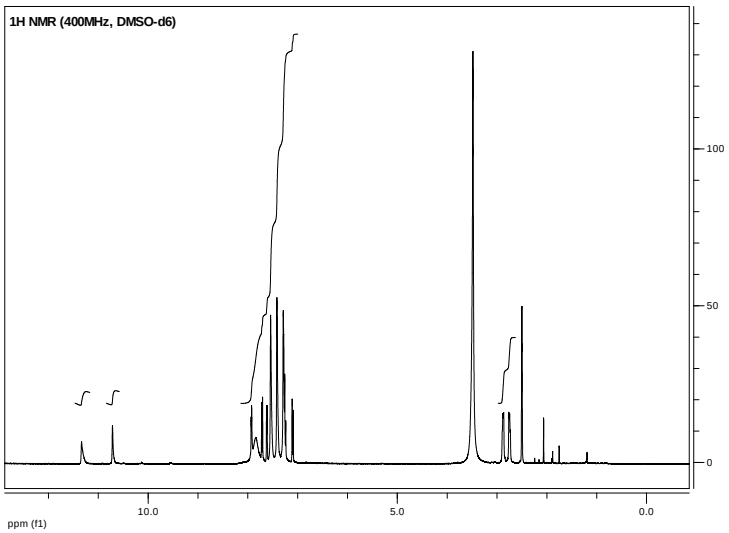
- **2-(5-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 36**

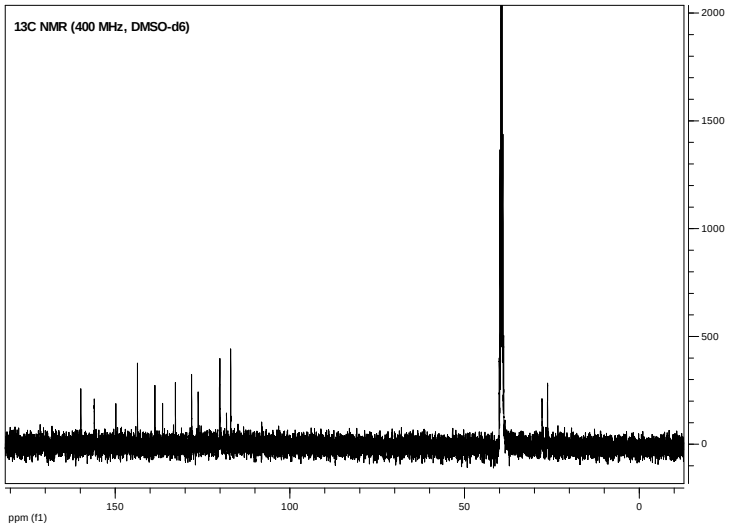


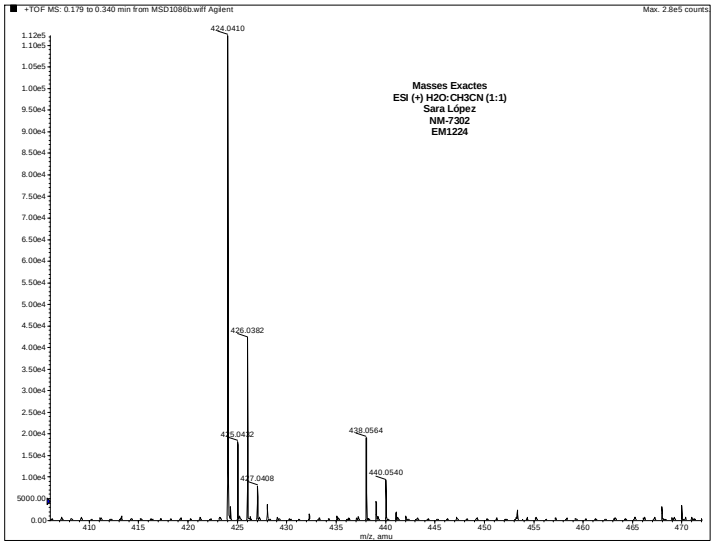



- **2-(4-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-ylidene)hydrazinecarboximidamide hydrochloride 37**

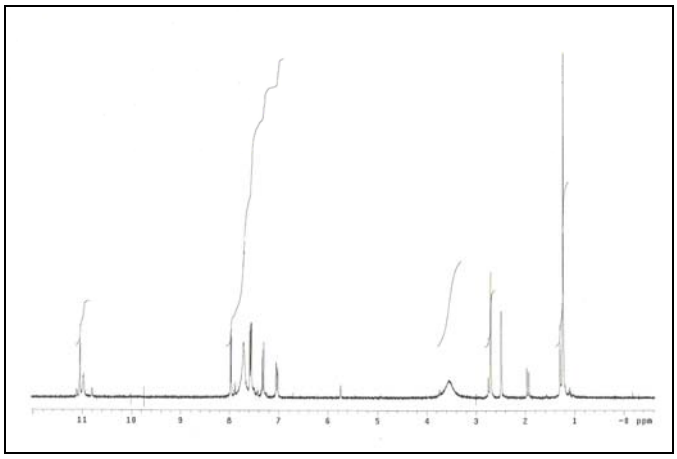


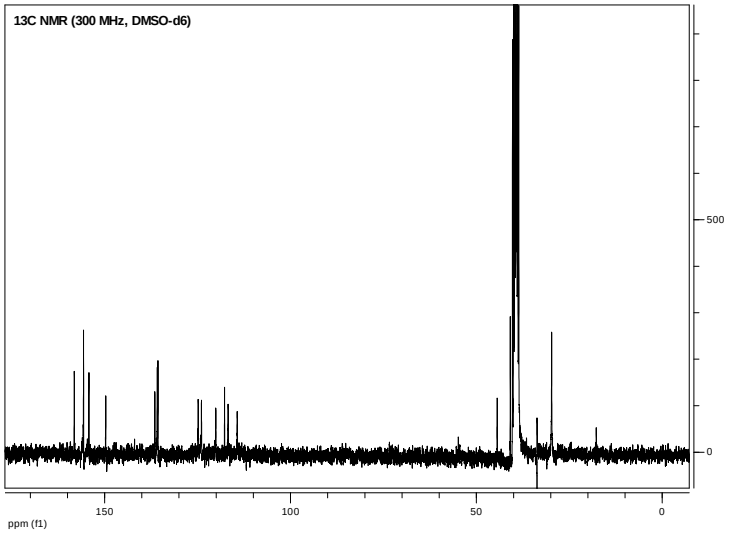



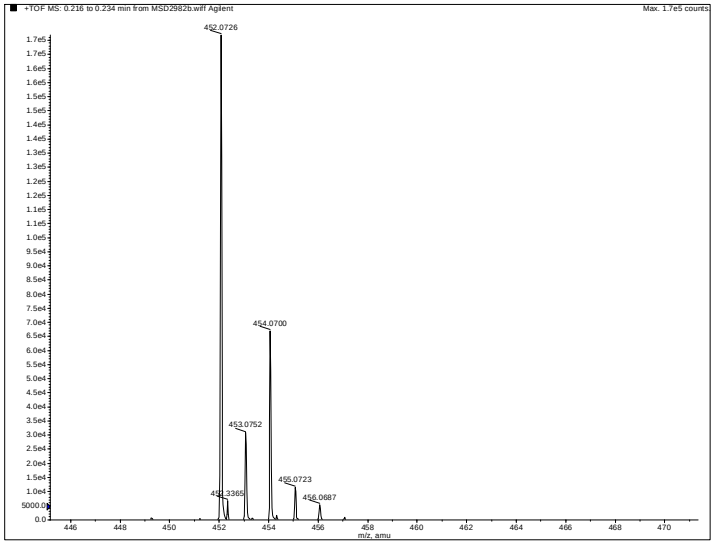



- **2-(6-{[(6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 38**

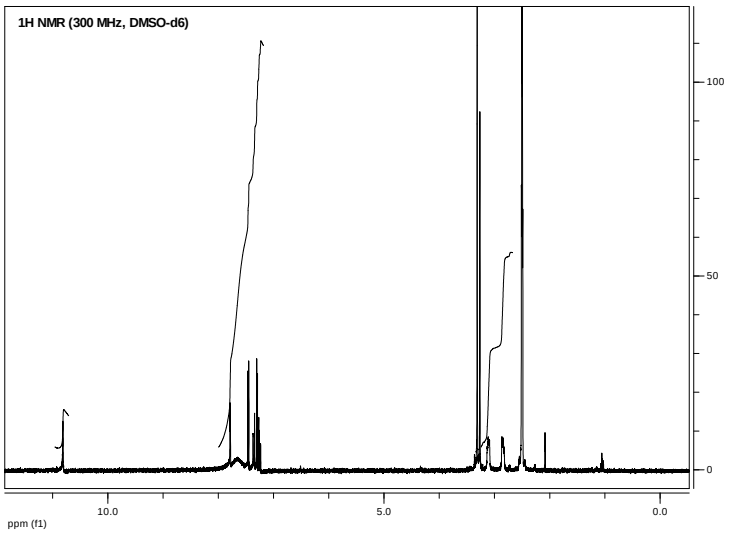
$^{1}$H NMR (300 MHz, DMSO-$d_6$)

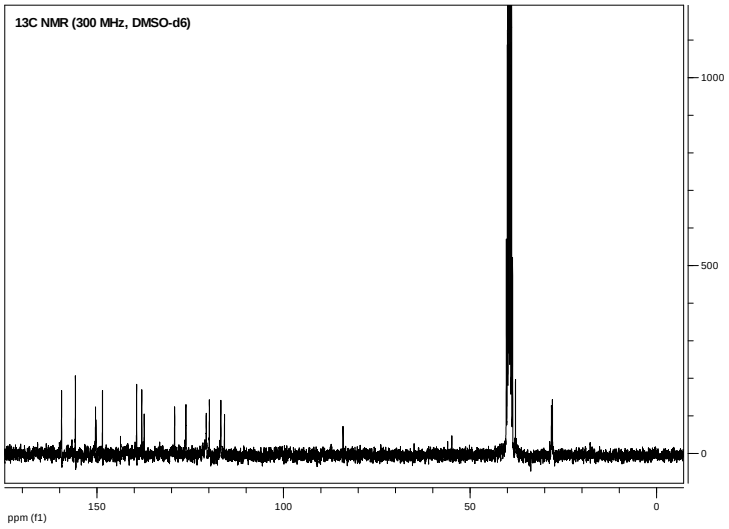


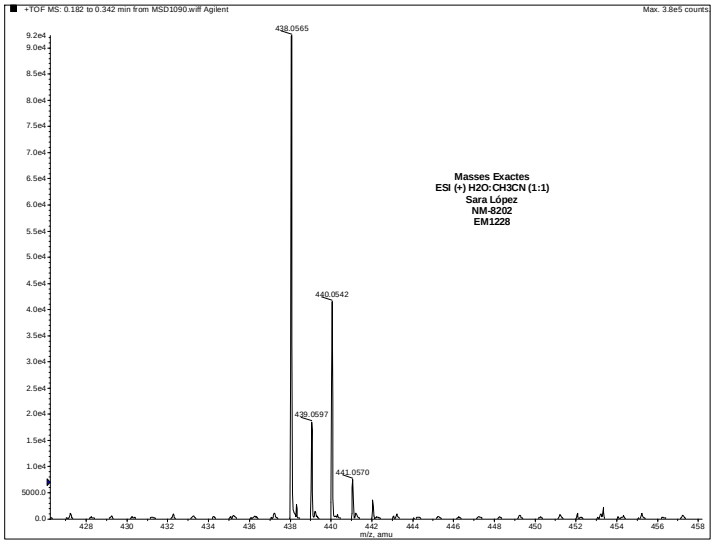


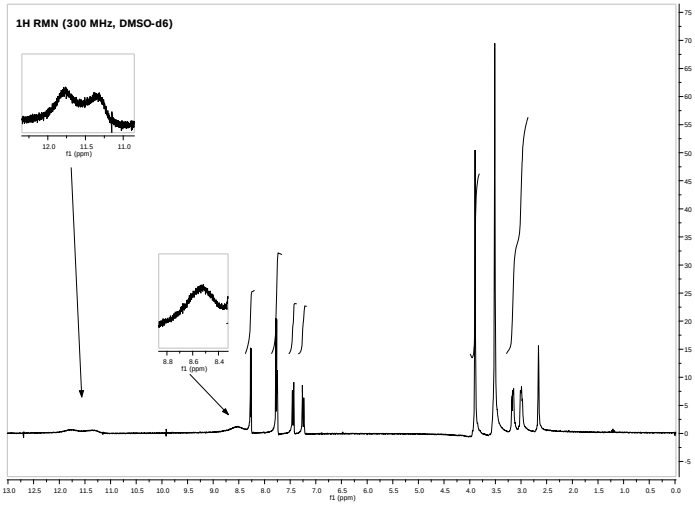
- **2-(6-{[(6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl](methyl)amino}-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 39**

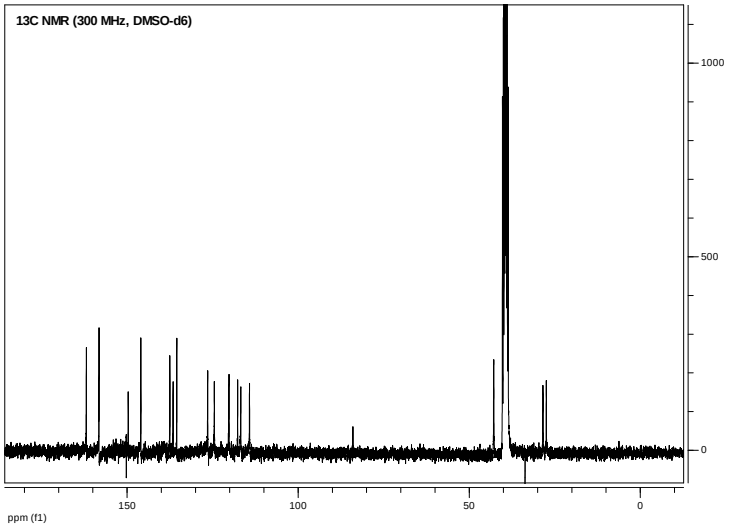


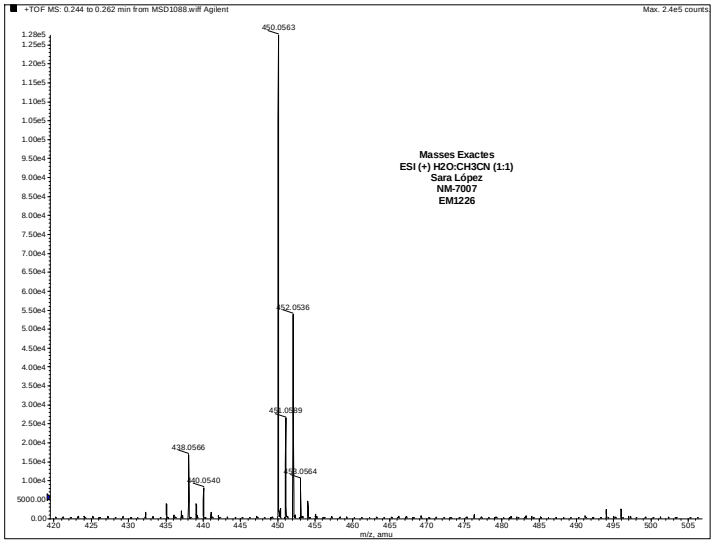



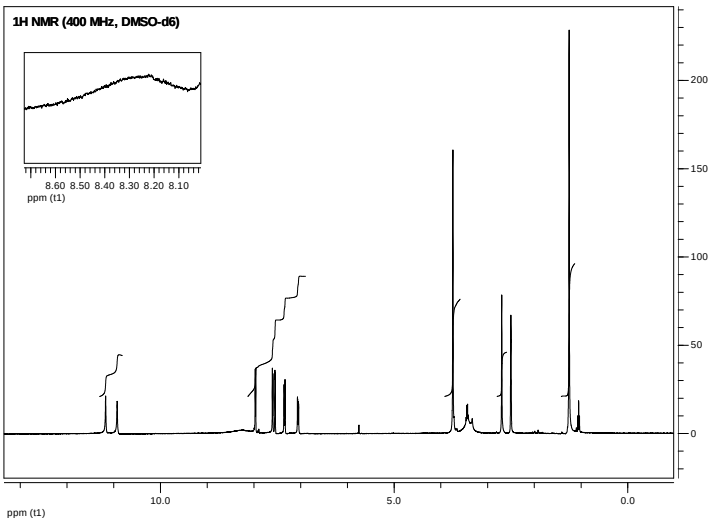
- **6-chloro-*N*-[3-(4,5-dihydro-1*H*-imidazol-2-ylhydrazono)-2,3-dihydro-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide hydrohalide 40**

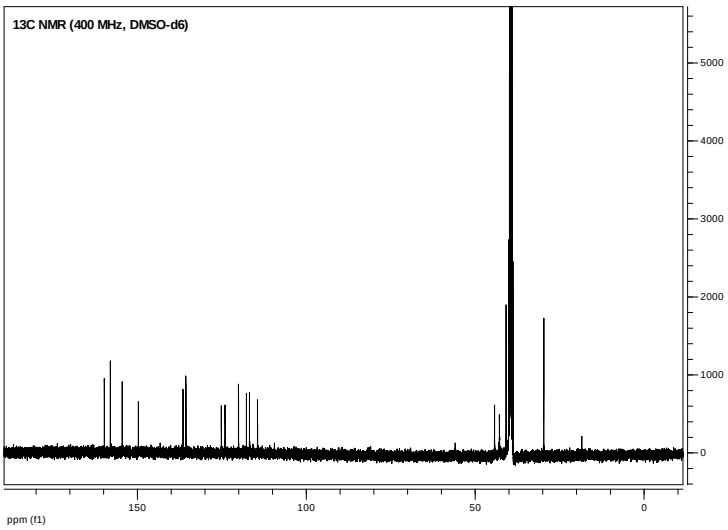


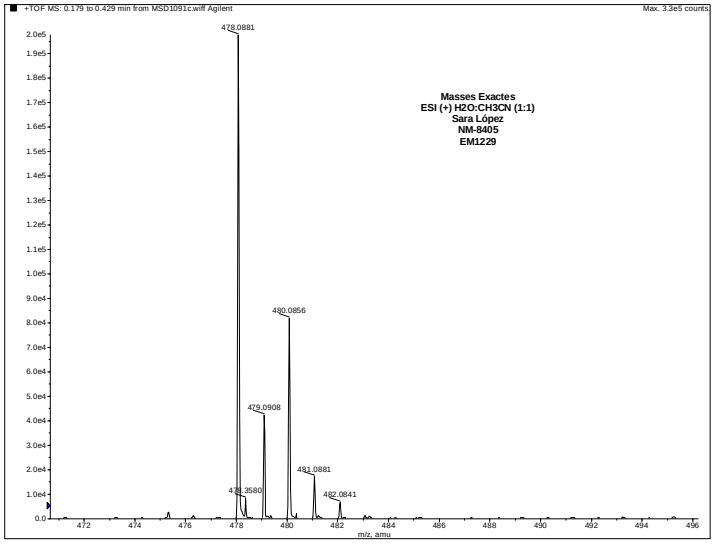



- **6-Chloro-*N*-[3-(4,5-dihydro-1*H*-imidazol-2-ylhydrazono)-1,1-dimethyl-2,3-dihydro-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide hydrohalide 41**



## 6.4. Patents

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(74) Agent: **CARPINTERO LOPEZ, Francisco**; Herrero & Asociados, S.L., Alcala, 35, E-28014 Madrid (ES).

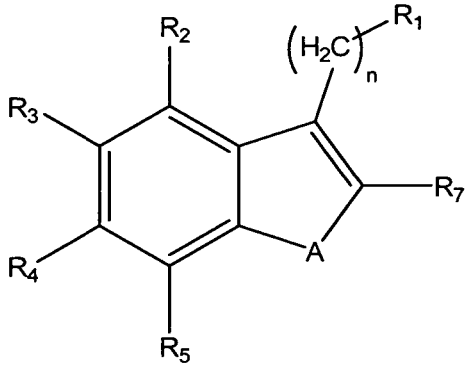
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: INDENE DERIVATIVES, THEIR PREPARATION AND USE AS MEDICAMENTS




(I)

(57) Abstract: The present invention makes reference to new indene derivatives with general formula (I), as well as to their preparation procedures, their application as medicament and the pharmaceutical compositions containing them. The new compounds of formula (I) show affinity for 5-$HT_6$ receptors and are, therefore, effective for treating diseases mediated by these receptors.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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International Bureau

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PCT/EP2007/057658

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(71) Applicant *(for all designated States except US)*: **LABORATORIOS DEL DR. ESTEVE, S.A.** [ES/ES]; Avda. Mare de Deu de Montserrat, 221, E-08041 Barcelona (ES).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FRIGOLA-CONSTANSA, Jordi** [ES/ES]; Avda. Mare de Deu de Montserrat, 221, E-08041 Barcelona (ES). **HOLENZ, Joerg** [DE/ES]; Avda. Mare de Deu de Montserrat, 221, E-08041 Barcelona (ES). **MERCE-VIDAL, Ramon** [ES/ES]; Avda. Mare de Deu de Montserrat, 221, E-08041 Barcelona (ES). **ALCALDE-PAIS, Maria, de las Ermitas** [ES/ES]; Facultad de Farmacia, Universidad de Barcelona, Avda. Joan XXIII, s/n, E-08028 Barcelona (ES). **MESQUIDA-ESTEVEZ, Maria, de les Neus** [ES/ES]; Facultad de Farmacia, Universidad de Barcelona, Avda. Joan XXIII, s/n, E-08028 Barcelona (ES). **LOPEZ-PEREZ, Sara** [ES/ES]; Facultad de Farmacia, Universidad de Barcelona, Avda. Joan XXIII, s/n, E-08028 Barcelona (ES).

(74) Agent: **CARPINTERO LOPEZ, Francisco**; Herrero & Asociados, S.L., Alcala, 35, E-28014 Madrid (ES).

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**Published:**
— *without international search report and to be republished upon receipt of that report*

WO 2008/015137 A2

(54) Title: SUBSTITUTED INDANYL SULFONAMIDE COMPOUNDS, THEIR PREPARATION AND USE AS MEDICAMENTS

(57) Abstract: The present invention refers to new indanyl sulphonamide compounds with general formula (I), as well as to their preparation procedure, their application as medicine and the pharmaceuticals composition which they are made up of. The new compounds of formula I show affinity for 5-$HT_6$ receptors and are, therefore, effective for treating diseases mediated by these receptors.