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-

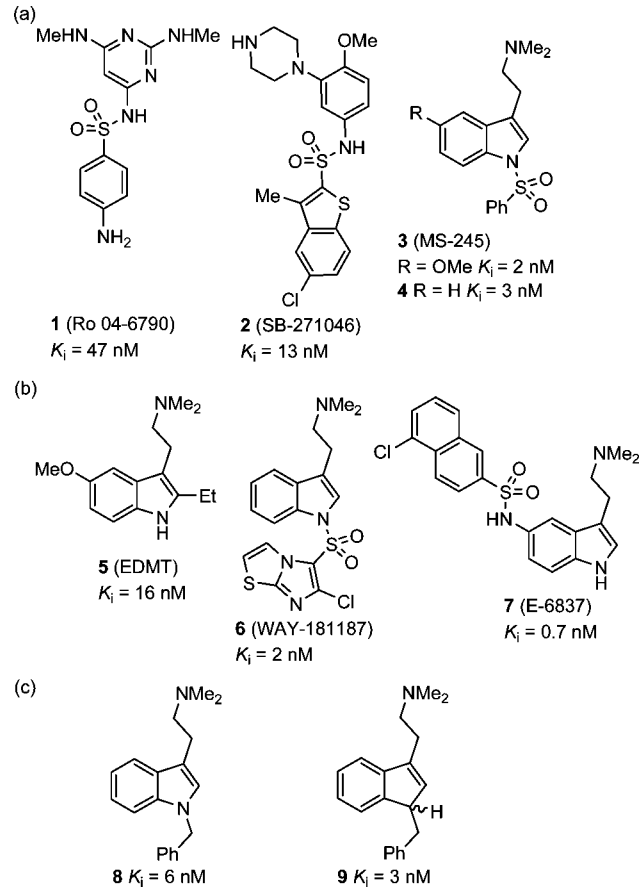

Figure 1. Several examples of 5-HT$_6$ serotonin receptor ligands: (a) antagonists **1**−**4**, (b) agonists **5**−**7**, (c) indole-indene compound pairs **8** and **9**.

[†] Part 1: ref 1.

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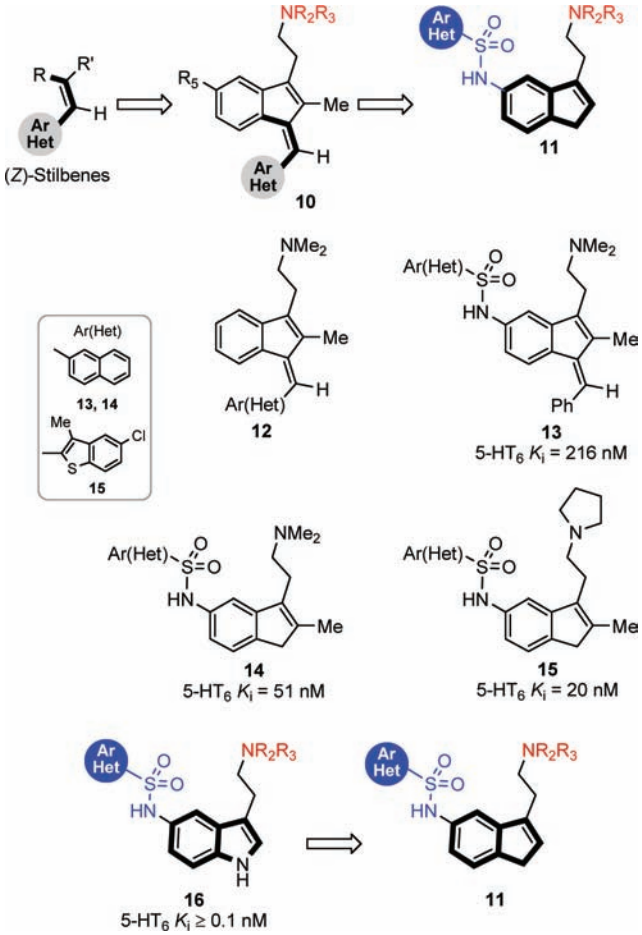


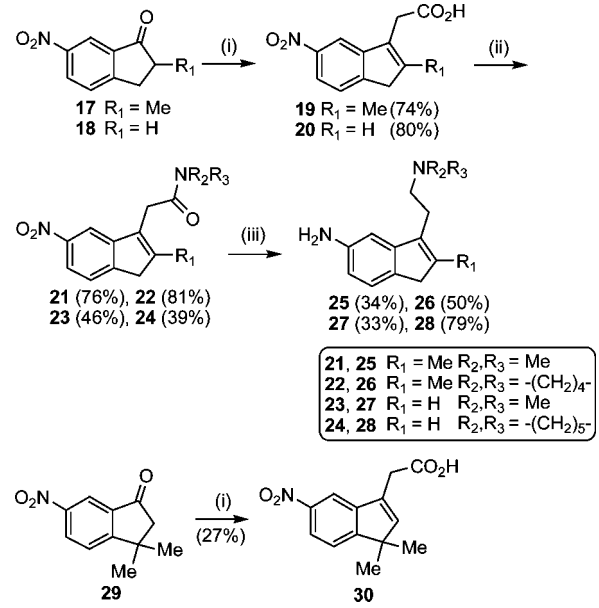
Figure 2. Design of 5-HT_6 serotonin receptor ligands: from (*Z*)-arylmethylideneindenes **10** to indenylsulfonamides **11**.

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]



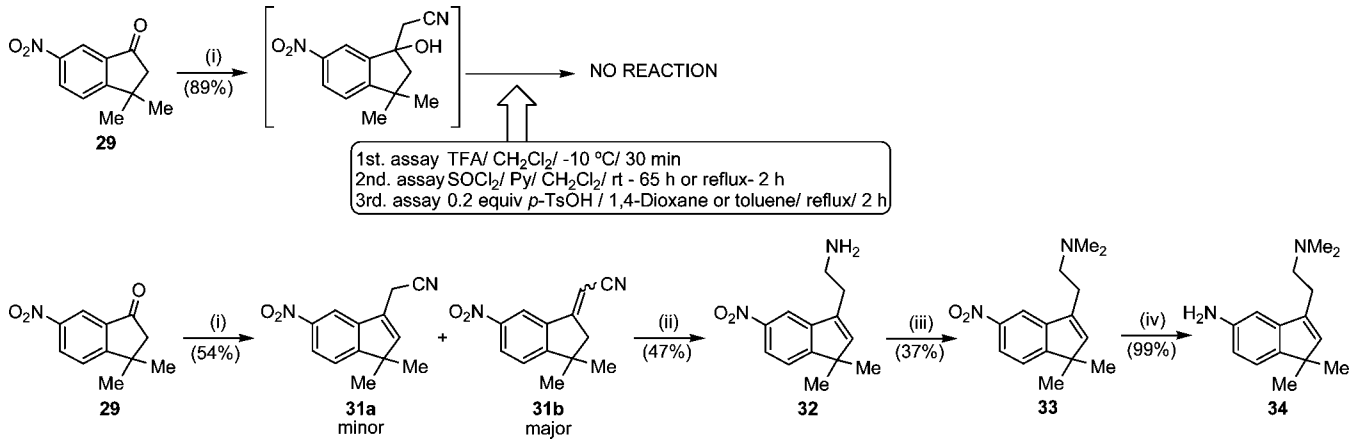
[a] Reagents and conditions: (i) (a) EtOAc, LHMDS, THF, −78 °C, (b) H_2SO_4, H_2O, 60 °C; (ii) (a) $SOCl_2$, CH_2Cl_2, reflux, (b) Me_2NH, pyrrolidine or piperidine, rt; (iii) (a) AlH_3−NMe_2Et, THF, 0 °C, (b) Zn, AcOH, rt.

≥4.5 nM and acting as 5-HT_6 receptor agonists. Notably, the scaffold was modified by satisfactorily replacing an indole (a π-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**.

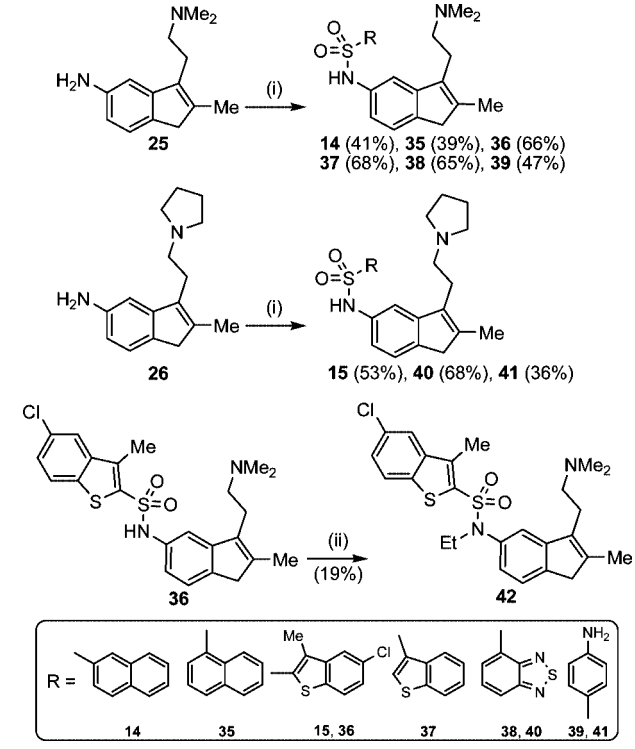
Chemistry. *N*-(Inden-5-yl)sulfonamides of general type **11** were synthesized following multistep procedures from suitable nitroindanones to the corresponding key inden-5-amines, which enabled us to diversify the synthesis of a variety of indenylsulfonamides **11** on the 5-position. As a starting 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]



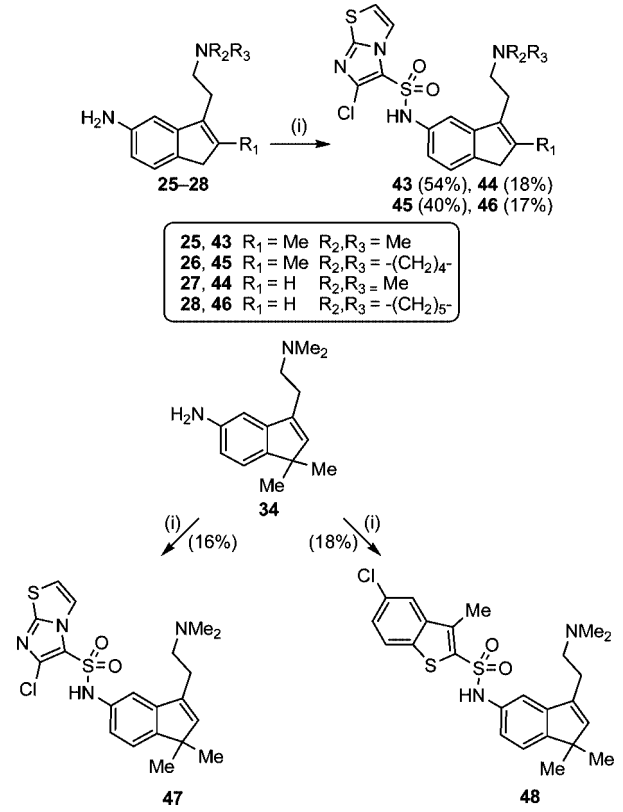
[a] Reagents and conditions: (i) (a) *n*-BuLi, MeCN, THF, −78 °C, (b) *p*-TsOH·H_2O, toluene, 150 °C; (ii) (a) AlH_3−NMe_2Et, THF, rt, (b) HCl, EtOH, 70 °C; (iii) HCOH, $NaBH_3CN$, AcOH, MeCN, rt; (iv) Zn, AcOH, rt.

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.

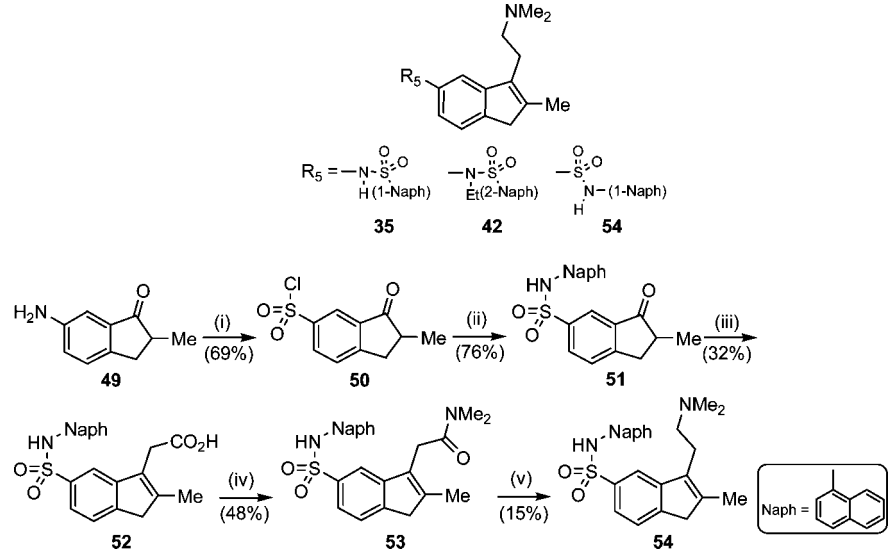
Then the nitro group was reduced with zinc in glacial acetic acid to afford the inden-5-amines **25**−**28**. Under the best reaction conditions and reagents, compounds **25**−**28** were prepared in 12−30% overall yields.

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

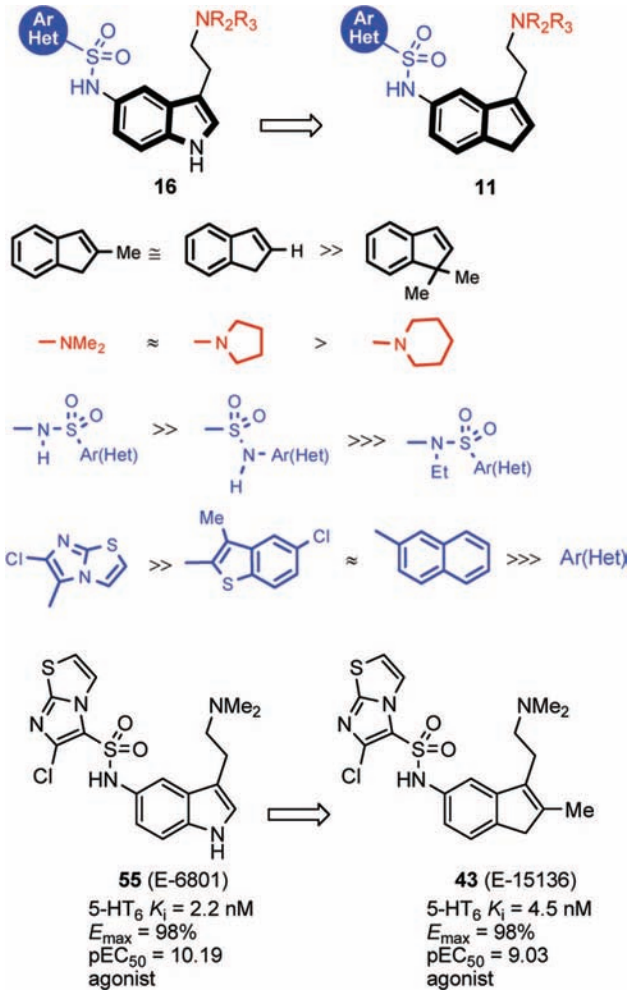


Figure 3. Indole-to-indene core change: from indolylsulfonamides **16** to indenylsulfonamides **11**.

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 (δ) 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 (δ) 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 μ, 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; λ = 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) 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): ν(COO-H) 3090; ν(C═O) 1703; $\nu(NO_2)$ 1515, 1332 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 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): δ 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): ν(COO-H) 3106; ν(C═O) 1700; $\nu(NO_2)$ 1510, 1343 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 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): δ 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): ν(N−C═O) 1641; $\nu(NO_2)$ 1515, 1342 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 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): δ 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); ν(N−C═O) 1624; $\nu(NO_2)$ 1513, 1336 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 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): δ 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): ν(N−C═O) 1641; $\nu(NO_2)$ 1512, 1345 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 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): δ 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): ν(N−C═O) 1618; $\nu(NO_2)$ 1518, 1345 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 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): δ 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, $CDCl_3$): δ 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): δ 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, $CDCl_3$): δ 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): δ 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, $CDCl_3$): δ 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): δ 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, $CDCl_3$): δ 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): δ 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): ν(COO-H) 3090; ν(C═O) 1682; $\nu(NO_2)$ 1630 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ 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): δ 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): ν(CN) 2209; $\nu(NO_2)$ 1523, 1345 cm^{-1}. ^1H (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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): δ 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, $CDCl_3$): δ 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): δ 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, $CDCl_3$): δ 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): δ 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): ν(SO_2) 1320, 1158 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 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): δ 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): ν(NH) 3079; ν(SO_2) 1337, 1157 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 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): δ 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. ($C_{23}H_{25}ClN_2O_2S_2$·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): ν(NH) 3117; ν(SO_2) 1325, 1151 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 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): δ 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): ν(SO_2) 1335, 1158 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 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): δ 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. ($C_{20}H_{25}N_4O_2S_2$·$^1/_3H_2O$) 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): ν(NH_2) 3458; ν(NH) 3374; ν(SO_2) 1315, 1149 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 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): δ 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. ($C_{20}H_{25}N_3O_2S$·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): ν(NH) 3257; ν(SO_2) 1335, 1157 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 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): δ 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. ($C_{22}H_{24}N_4O_2S_2$·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; ν(NH) 3245; $\nu(SO_2)$ 1315, 1150 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 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): δ 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): ν(NH) 3117; $\nu(SO_2)$ 1343, 1136 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 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): δ 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): ν(NH) 3100; $\nu(SO_2)$ 1256, 1118 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 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): δ 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): ν(NH) 3112; $\nu(SO_2)$ 1244, 1118 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 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): δ 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): ν(NH) 3124; $\nu(SO_2)$ 1228, 1112 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 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): δ 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, $CDCl_3$): δ 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): δ 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): ν(NH) 3151; $\nu(SO_2)$ 1332, 1159 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 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): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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): δ 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): ν(NH) 3274; ν(C═O) 1703; ν(SO_2) 1350, 1159 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 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): δ 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].

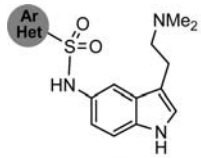
{2-Methyl-5-[(1-naphthylamino)sulfonyl]-1*H*-inden-3-yl}acetic acid 52. Dry EtOAc (0.300 mL, 2.87 mmol) was added dropwise to a stirred solution of LHMDS (1.0 M in THF, 5.80 mL, 5.80 mmol) in dry THF (3 mL) at −78 °C under argon atmosphere. After 15 min, a solution of indanone sulfonamide **51** (0.960 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): ν(NH) 3251; ν(COO-H) 3251; ν(C═O) 1710; ν(SO_2) 1311, 1151 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 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): δ 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): ν(NH) 3056; ν(C═O) 1630; ν(SO_2) 1314, 1151 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 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): δ 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].

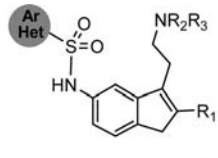
3-[2-(Dimethylamino)ethyl]-2-methyl-*N*-naphth-1-yl-1*H*-indene-5-sulfonamide 54. On a sufficient amount of dry THF cooled to 0 °C, AlH_3−NMe_2Et (0.5 M in toluene, 0.600 mL, 0.300 mmol) was added. Then a solution of acetamide derivative **53** (70.0 mg, 0.170 mmol) in dry THF (5 mL) cooled to 0 °C was 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): ν(NH) 3021; ν(SO_2) 1316, 1151 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 200 MHz ($CDCl_3$): δ 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): δ 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 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. 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

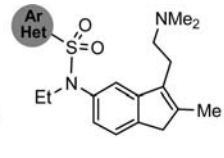
Table 1. 5-HT_6 Receptor Affinity and Functionality of Compounds **7**, **14**, **15**, **35**, **37**−**48**, **54**, and **55**



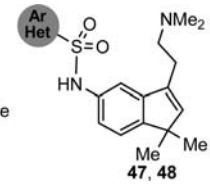
7, **55**



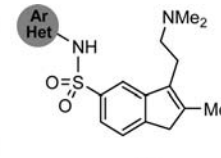
14, **15**, **35**, **37**–**41**, **43**–**46**



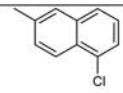
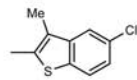
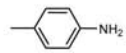
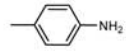
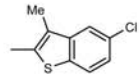
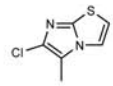
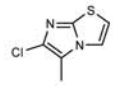
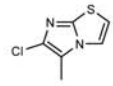
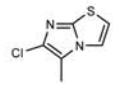
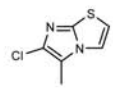
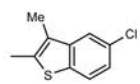
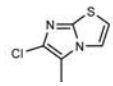
42



47, **48**

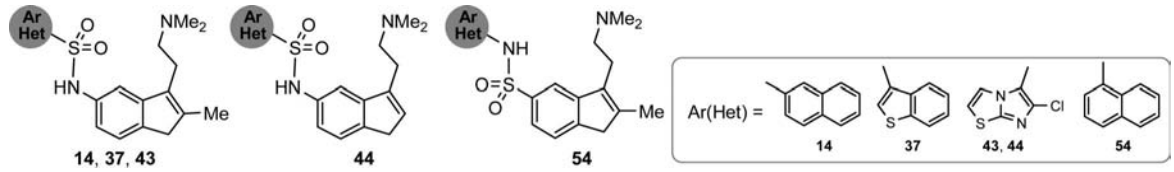


54

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 μM = 100. [g] % Inhib @ 1 μM = 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	α_1-adrenoceptor[a] IC_{50} (nM)	α_{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 μM pargyline. Then 40 μL 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 the 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).[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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