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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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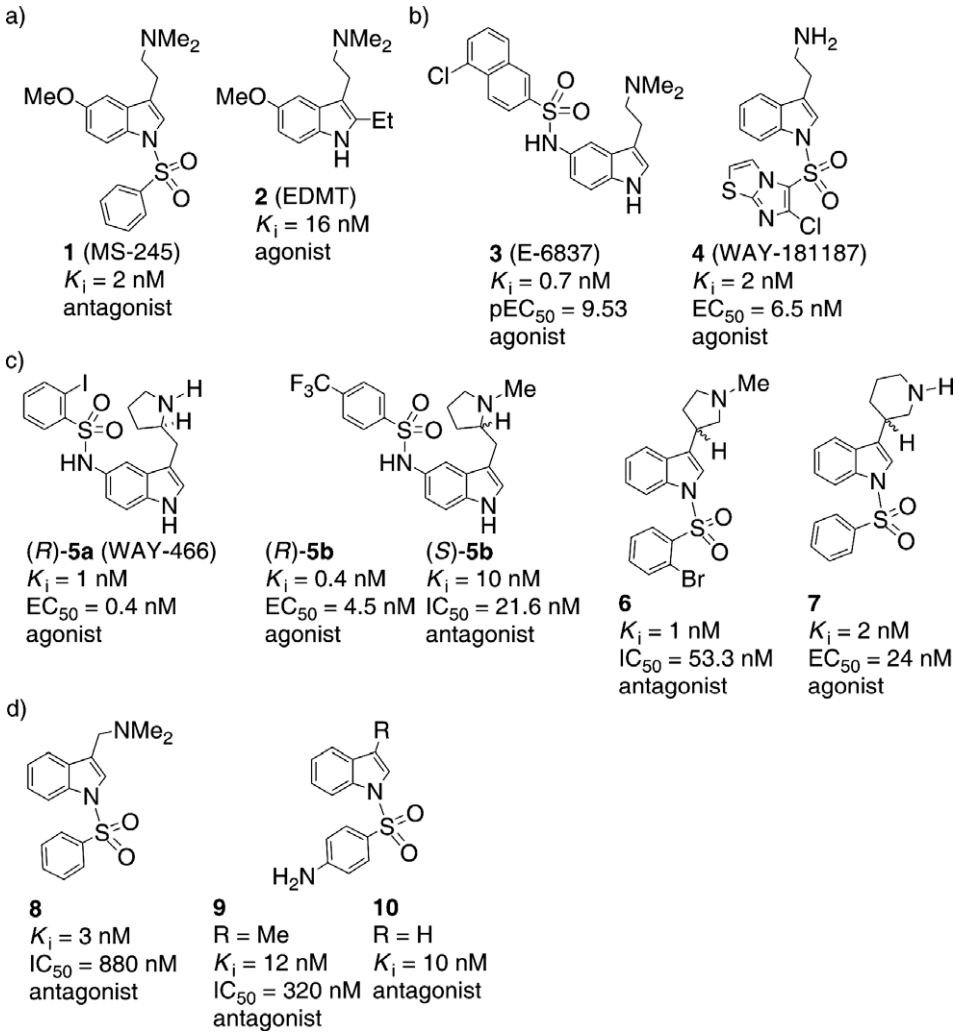


Figure 1. Indole-based 5-HT_6 serotonin receptor ligands: (a) early reference compounds, antagonist **1** (MS-245) and agonist **2** (EDMT); (b) examples of selective agonists **3** (E-6837) and **4** (WAY-181187); (c) conformationally constrained aminoethyl side chain in sulfonyltryptamines (*R*)-**5a** (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**

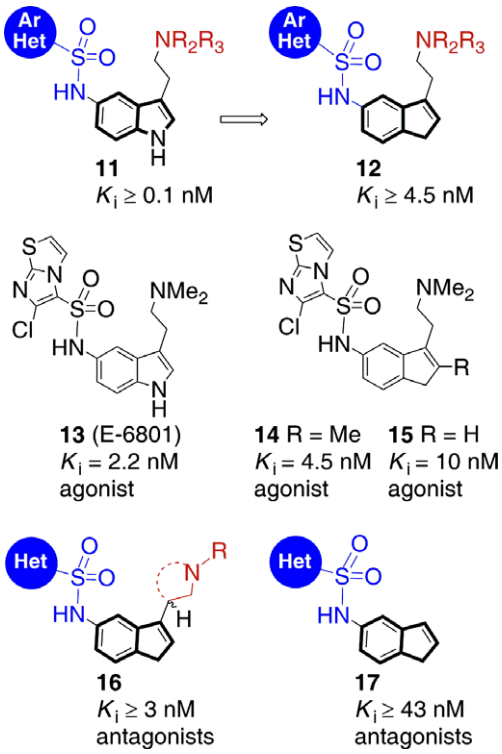


Figure 2. *N*-(Inden-5-yl)sulfonamides as novel 5-HT_6 serotonin receptor ligands: from *N*-[3-(aminoethyl)inden-5-yl]sulfonamides **12** to the conformationally rigid counterparts **16** and the structurally simplified *N*-(inden-5-yl)sulfonamides **17**.

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).

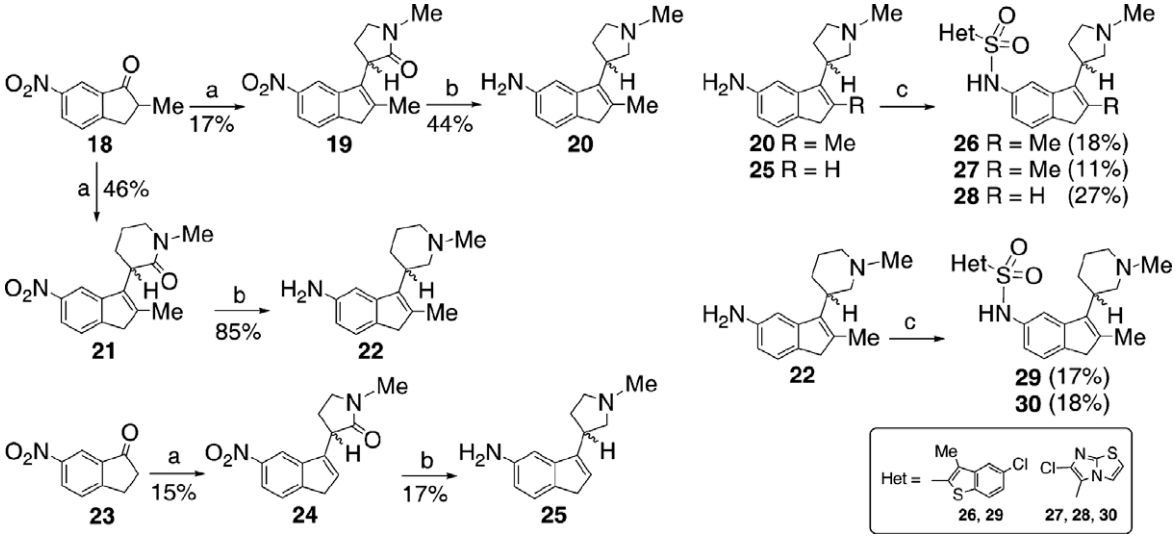
Depending on the difficulties encountered in the isolation and purification, chromatographic separations were generally required and sometimes a second chromatographic run was necessary. The quantity of new targeted compounds was variable but sufficient for the preliminary testing of their 5-HT_6 receptor 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.

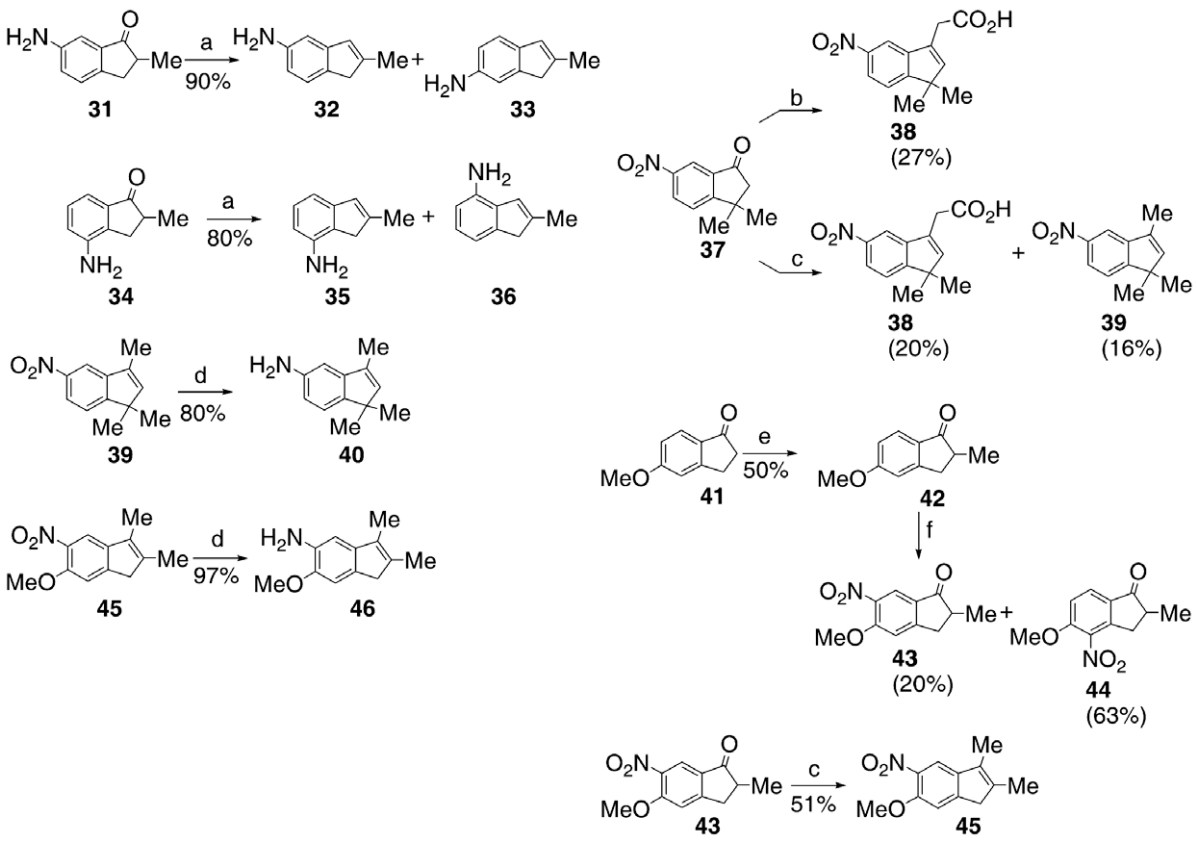
In the ^{1}H NMR spectra recorded in $CDCl_3$ and DMSO-d_6 at 400 MHz, respectively, for the mixture of isomers **47** + **48**, the overlapping peaks could not be differentiated. However, the ^{1}H NMR data in $CDCl_3$ at 600 MHz allowed the isomer **47** to be distinguished from **48** with the following 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.

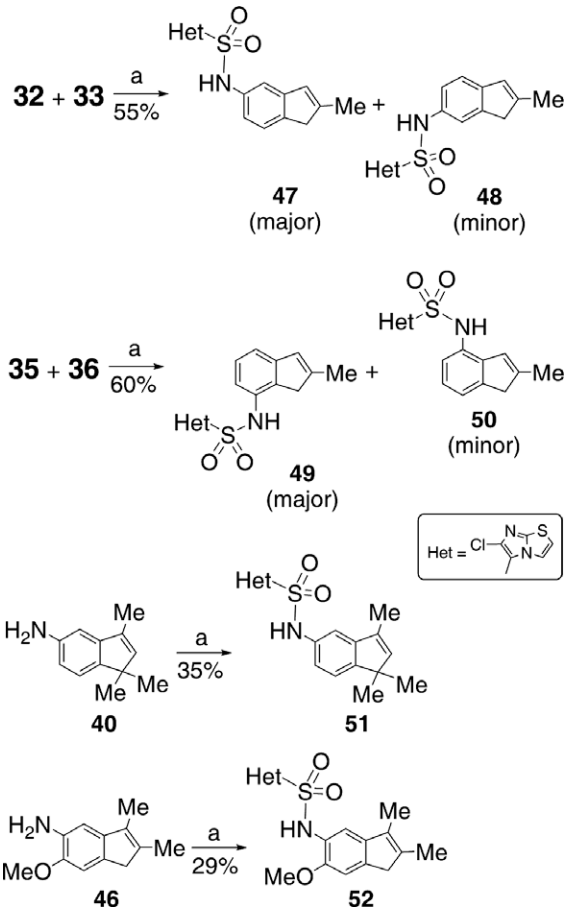


Scheme 2. Reagents and conditions: (a) (i) $NaBH_4$, EtOH, room temperature, (ii) 50% H_2SO_4, MeOH, 100 °C; (b) (i) EtOAc, LHMDS, THF, −78 °C, (ii) 50% H_2SO_4, 60 °C (see Ref. 1); (c) (i) EtOAc, LHMDS, THF, −78 °C, (ii) 50% H_2SO_4, 70 °C or 100 °C; (d) Zn, AcOH, room temperature; (e) (i) LDA, THF/DME,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

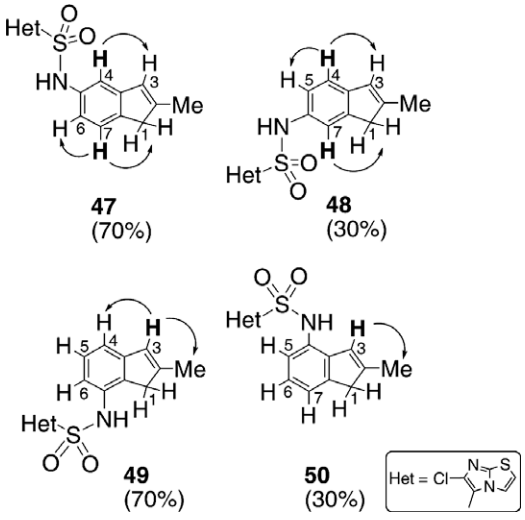
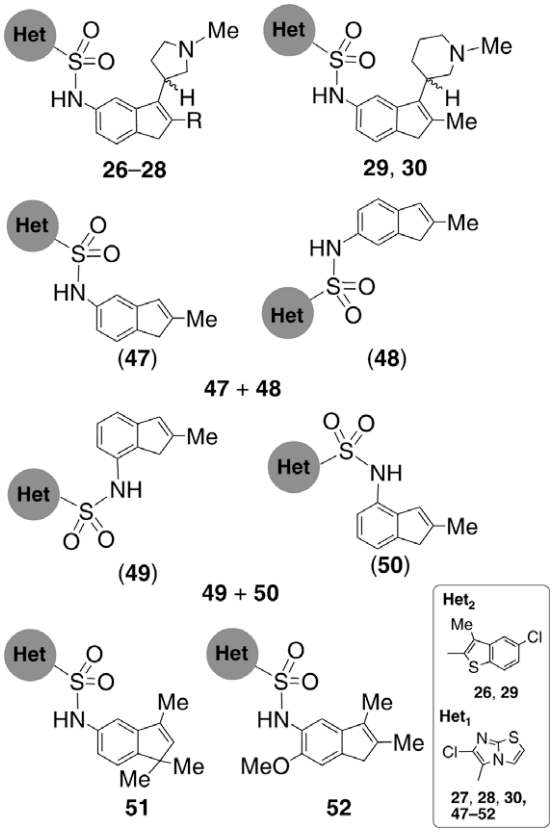


Figure 3. Isomer distribution and key NMR responses for the isomeric mixtures of *N*-(indenyl)sulfonamides **47** + **48** and **49** + **50**: 1D NOESY experiments.

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**



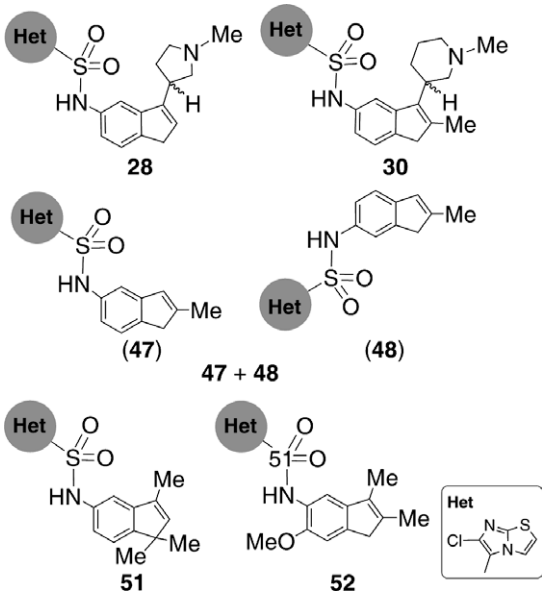
Compd	R	Het	% Inhib. @ 100 nM	K_i[a] (nM)	I_{max}[b] (%)	IC_{50}[b] (μM)
26	Me	Het_2	57			
27	Me	Het_1	ND			
28	H	Het_1	92	3.0	100	1.6
29	Me	Het_2	22			
30	Me	Het_1	86	18	28	
47 + **48**[c]	Me	Het_1	78	43	75	3.0
49 + **50**[d]	Me	Het_1	5			
51	H	Het_1	75	80	92	2.4
52[e]	Me	Het_1	84	64	10	

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	α_1[a] IC_{50} (nM)	α_{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 α_1-adrenoceptor.
[b] Human α_{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 (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). 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; 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).

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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(C=O) 1672, ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(C=O) 1637, ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(C=O) 1670, ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): δ = 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): ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(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, $CDCl_3$): δ = 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): δ = 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): ν(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, $CDCl_3$): δ = 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, $CDCl_3$,): δ = 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): ν(OCH_3) 2842, 1252; ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(OCH_3) 2872, 1299, ν(C=O) 1715; ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ 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): ν(OCH_3) 2874, 1259; ν(C=O) 1713, ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(OCH_3) 2915, 1268, ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(NH) 3394; ν(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, $CDCl_3$): δ = 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): δ = 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): ν(NH) 3128, ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(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, $CDCl_3$): δ = 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): δ = 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): ν(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, $CDCl_3$): δ = 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): δ = 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): ν(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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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): ν(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, $CDCl_3$): δ = 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): δ = 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): ν(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]

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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.

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