Indene-based scaffolds. Design and synthesis of novel serotonin 5-HT$_6$ receptor ligands†

Ermitas Alcalde,*[a] Neus Mesquida,*[a] Jordi Frigola,[b] Sara López-Pérez[a] and Ramon Mercè[b]

Received 21st May 2008, Accepted 11th July 2008
First published as an Advance Article on the web 11th August 2008
DOI: 10.1039/b808641a

A series of novel indene derivatives designed by a scaffold selection gave access to several examples of (*Z*)-arylmethylideneindenes and indenylsulfonamides that acted as serotonin 5-HT$_6$ receptor ligands. Different synthetic multistep routes could be applied to these target compounds, each with their own complexity and limitations. A reasonable route involved the (3-indenyl)acetic acids as the key intermediates, and two alternatives were also examined. The first protocol used was a two-step sequence employing a modified Horner–Wadsworth–Emmons reaction, but better results were obtained with a procedure based on the condensation of indanones with the lithium salt of ethyl acetate, followed immediately by dehydration with acid and hydrolysis/isomerization under basic catalysis. (3-Indenyl)acetic acids were transformed to the corresponding acetamides, which were effectively reduced to indenylsulfonamides **13–17** using an optimized procedure with AlH_3–NMe_2Et. The binding at the 5-HT$_6$ receptor was with moderate affinity (K_i = 216.5 nM) for the (*Z*)-benzylideneindenylsulfonamide **12** and enhanced affinity for the simple indenylsulfonamide counterpart **13** (K_i = 50.6 nM). Selected indenylsulfonamides **14–17** were then tested, showing K_i values as low as 20.2 nM.

Introduction

A survey of biologically active (*Z*)-stilbenes shows that (*Z*)-aryl(heteroaryl)methylideneindenes **1** form an ensemble of compounds with a variety of pharmacological profiles.[1] Relevant examples are the nonsteroidal anti-inflammatory drug (NSAID) sulindac **2** together with sulindac sulfone **3** and sulindac-derived compounds **4** (Fig. 1).[2] Exisulind **3** is a new class of targeted and pro-apoptopic drug, being the lead compound in a series of selective apoptotic antineoplasic drugs. A library of sulindac analogs **4** have led to new inhibitors of the tumor-relevant Ras signal transduction pathway, underlining the advantage of using biologically prevalidated compound classes in chemical biology research.[3,4] In an interesting study carried out concurrently with our own, Glennon and co-workers have examined the binding of several isotriptamines and indenes at the h5-HT$_6$ serotonin receptor, such as (*E*)-benzylideneindene **5** (K_i = 57 nM), (benzylindenyl)ethanamine **6** (K_i = 3 nM) and isotryptamine analog **7** (K_i = 32 nM), revealing that the indolic nitrogen atom is not essential for binding.[5]

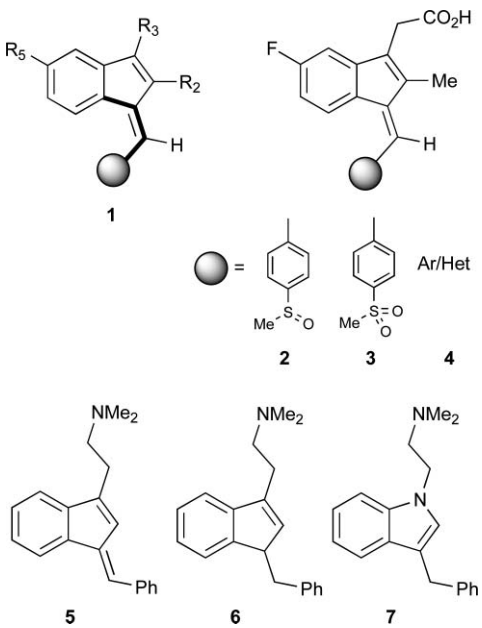


Fig. 1

As part of a project aimed at the study of (*Z*)-stilbenes with potential biological effects on the central nervous system (CNS), we focused our attention on an indene core of general type **1**, since indenes constitute a source of pharmacologically active molecules, and their synthesis and pharmacology have not yet been extensively explored. We thus hoped to maximise the likelihood of discovering compounds with biological properties. On the basis of these premises, the first series of indene compounds was based on the *cis*-indene structure **1** in which the (*Z*)-stilbene moiety was embedded and the traditional *N*,*N*-dimethylaminoethyl CNS functionality was incorporated at the 3-position. (*Z*)-Aryl(heteroaryl)methylideneindenes **8–11** were synthesized and compounds **10** and **11** were profiled against a panel of 64 radioligand binding assays along with the 5-HT$_6$

[a]*Laboratori de Química Orgànica, Departament de Farmacologia i Química Terapèutica, Facultat de Farmàcia, Universitat de Barcelona, Av. Joan XXIII s/n, E-08028, Barcelona, Spain. E-mail: ealcalde@ub.edu*
[b]*ESTEVE, Av. Mare de Déu de Montserrat, 221, E-08041, Barcelona, Spain*
† Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR assignments, NMR spectra of targeted compounds, assays related to the preparation of compounds **12–17**, **19**, **22** and **25**, and 5-HT$_6$ binding affinity and functionality (Table S1). See DOI: 10.1039/b808641a

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

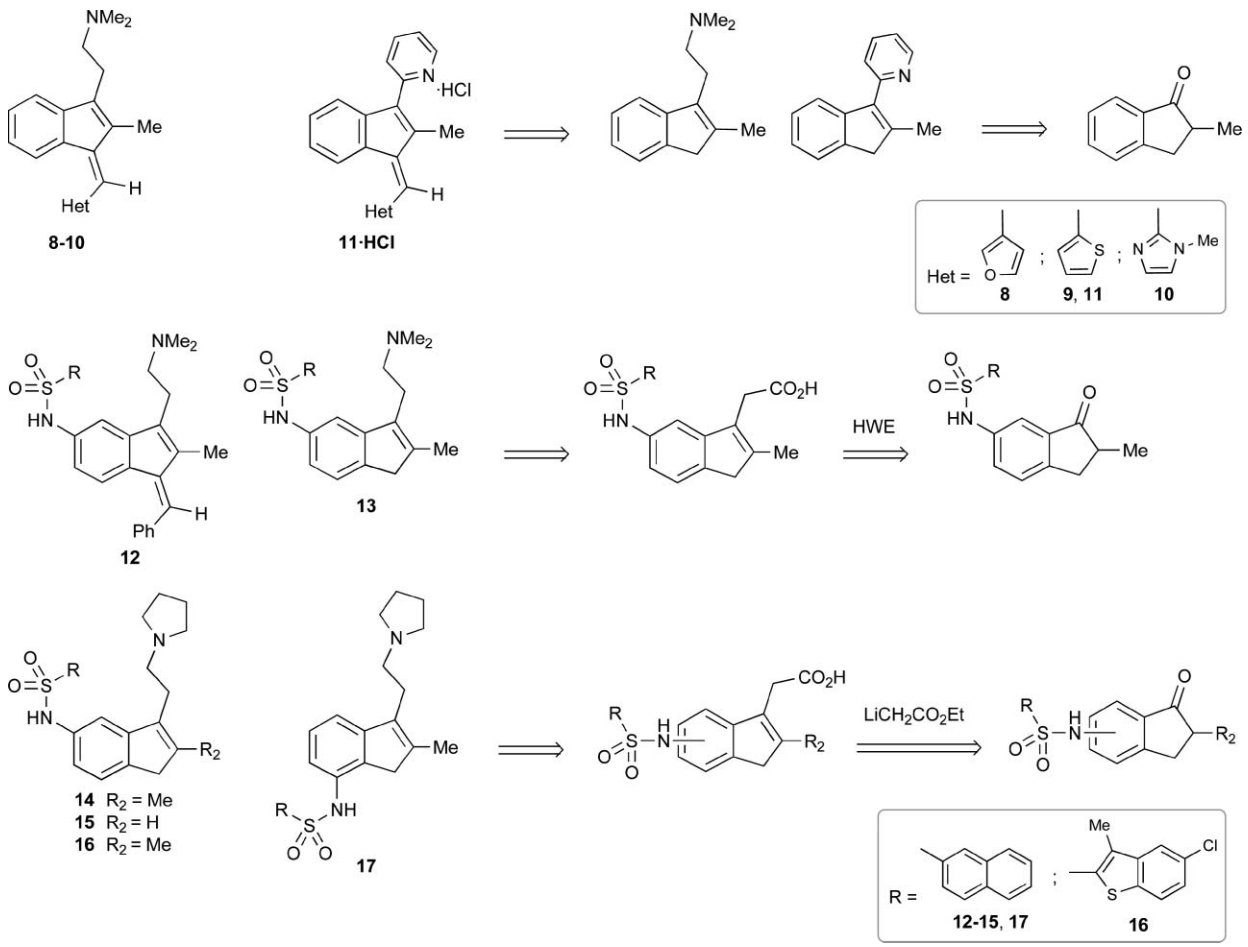
The subsequent design step was namely the incorporation of a sulfonamide group at the 5-position of the indene ring, since studies of 5-HT_6 serotonin receptor ligands have highlighted the importance of the sulfonyl moiety (*e.g.* sulfonamides, sulfones) for binding,[6] such as the series of indole-based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

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

Results and discussion

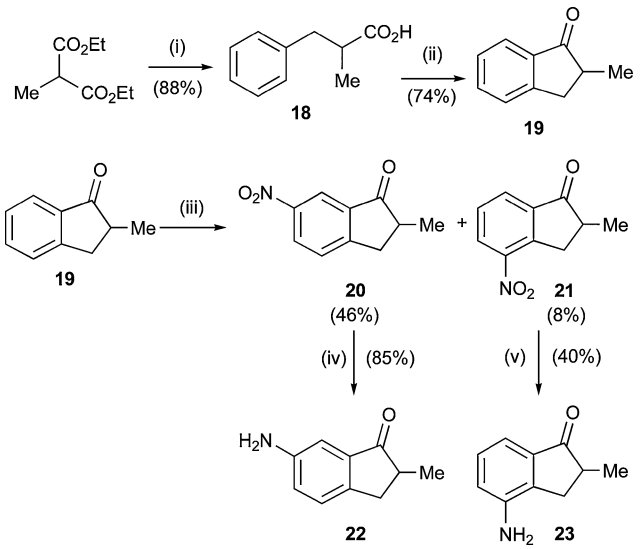
Chemistry

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



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

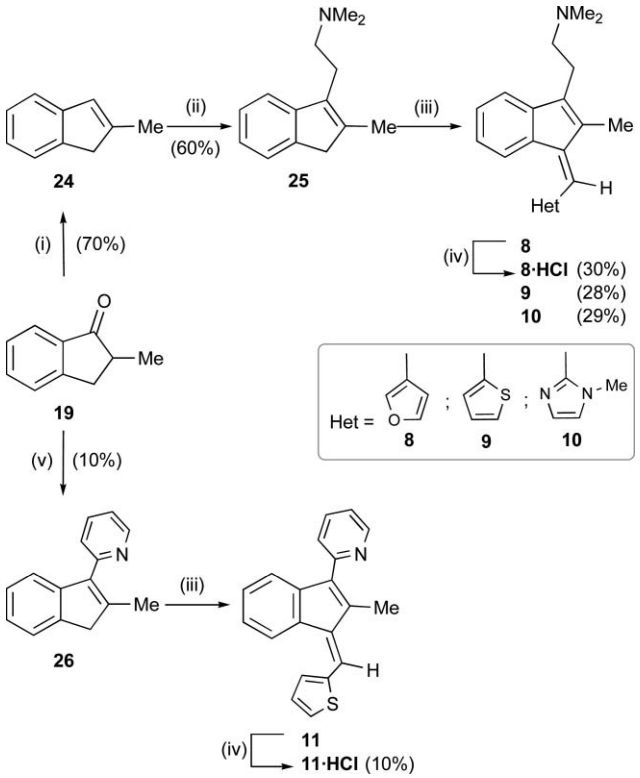
Preparation of substituted indan-1-ones started with a malonic-ester acid synthesis that gave the propanoic acid **18**, which was converted to the corresponding acid chloride and cyclized to 2-methylindan-1-one **19** under Friedel–Crafts reaction conditions (see ESI†). Nitration of **19** gave a mixture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



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

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

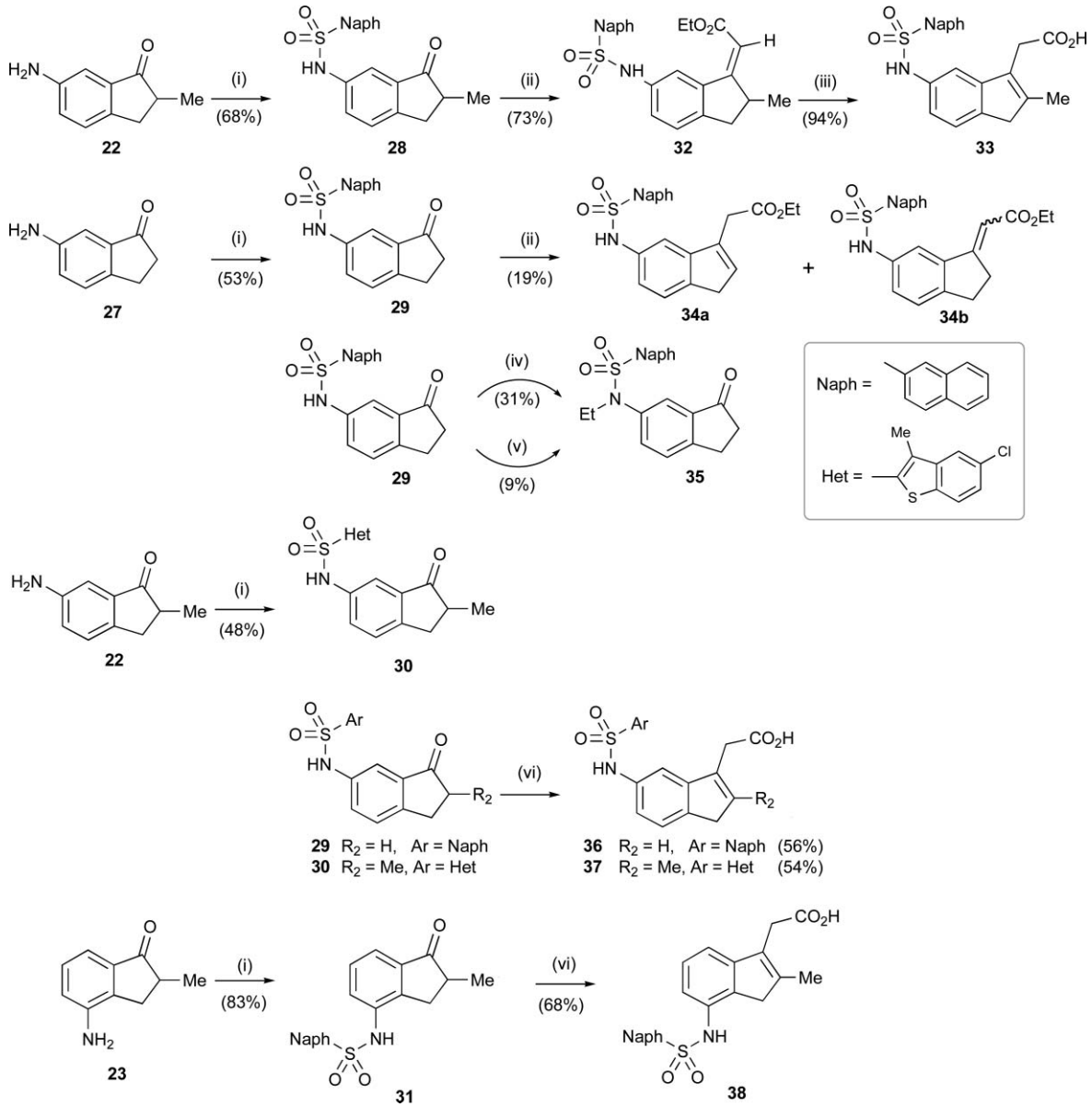
Although different multi-step synthetic routes could be applied to the target indenylsulfonamides **12–17**, a reasonable pathway appeared to involve (3-indenyl)acetic acids as the key intermediates (Scheme 1). Accordingly, preparation of the acetic acid derivatives started with the reaction of aminoindanones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



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

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

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



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

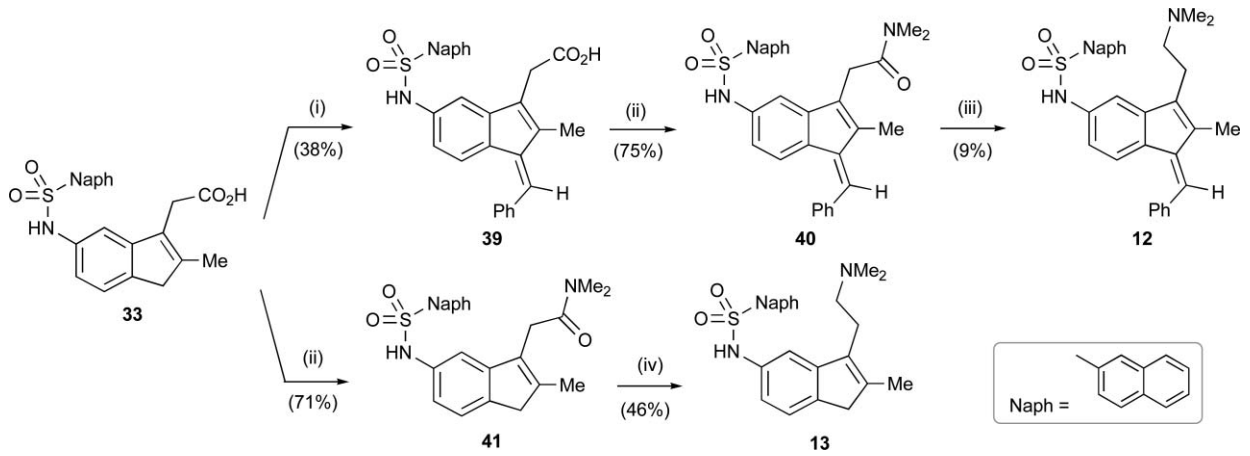
were transformed to the corresponding (3-indenyl)acetic acids **37** and **38** in good yields.

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

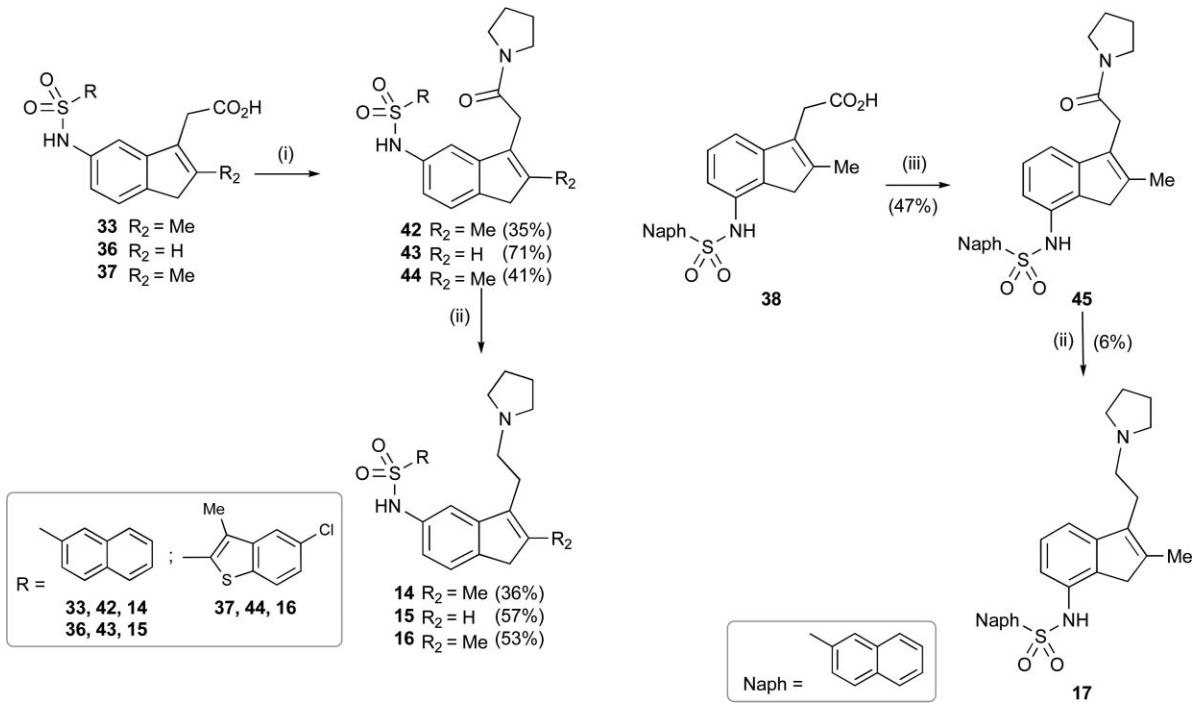
Following a similar stepwise synthetic route, indenylsulfonamides **14–17** were obtained from the corresponding (3-indenyl)-acetic acids **33** and **36–38** as shown in Scheme 6. Thus, compounds **33** and **36–38** were transformed to the corresponding amides **42–45**, which were effectively reduced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

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

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



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



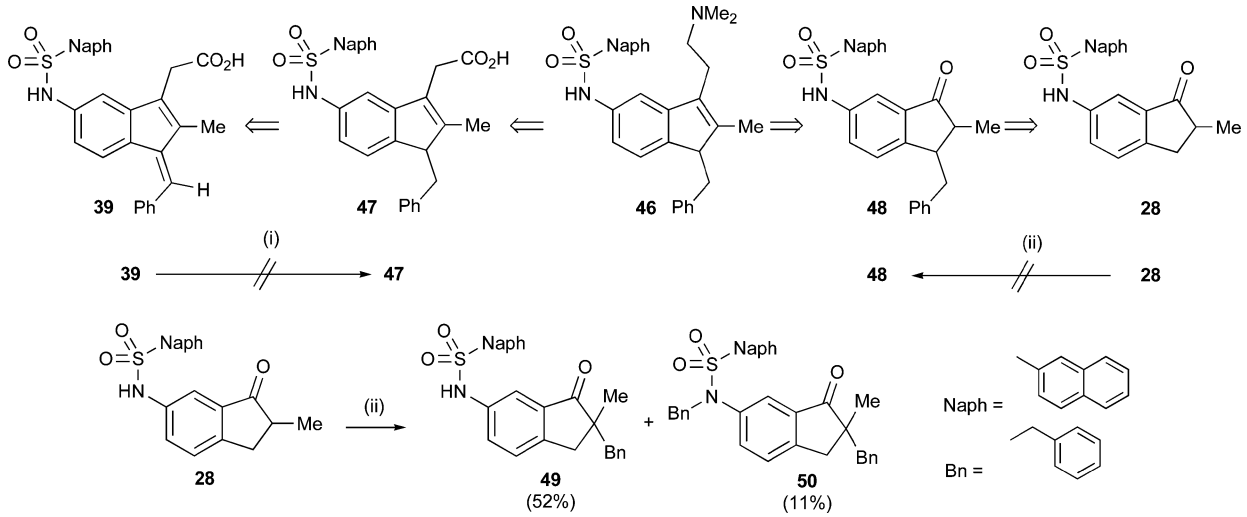
Scheme 6 *Reagents and conditions*: (i) (a) 1,1′-carbonyldiimidazole, THF, rt, (b) pyrrolidine, THF, rt; (ii) AlH_3–NMe_2Et, THF, 0 °C or rt; (iii) (a) $SOCl_2$, CH_2Cl_2, reflux, (b) C_4H_8NH, CH_2Cl_2, rt.

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

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

Biological results

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



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

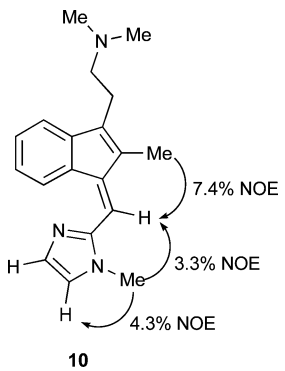


Fig. 2

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

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

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

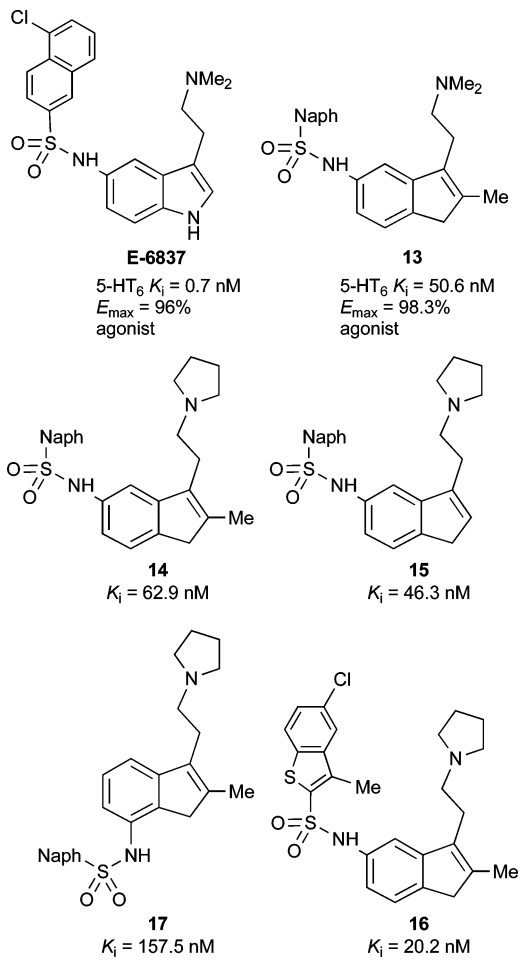


Fig. 3 Indole–indene core change: an approach toward high affinity and selective serotonin 5-HT_6 receptor ligands.

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

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

Conclusions

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

Experimental

General methods

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

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

Materials

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

2-Methylindan-1-one 19

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Synthesis of indanones sulfonamides 28–31: General procedure

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Synthesis of ethyl acetates 34a and 34b

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

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

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

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

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

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

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

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

Dry ethyl acetate (1.05 equiv) was added dropwise to a stirred solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 2.1 equiv) at −78 °C. After 15 min, a solution of indanone sulfonamides **29**, **30** or **31** (1 equiv) in dry THF was added dropwise and the mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched by addition of 1 N HCl and was warmed to ambient temperature. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were evaporated to dryness. Trifluoroacetic acid (7 equiv) was added dropwise to a stirred solution of the resulting residue in dry CH_2Cl_2 at −5 °C. After 35 min, the mixture was concentrated in vacuum. To a stirred solution of the resultant foamy solid in dry MeOH at room temperature was added sodium (4 equiv) in dry MeOH under argon atmosphere. The resulting mixture was refluxed for 24 h. To cooled reaction mixture EtOH was added dropwise, and the mixture then evaporated. To the residue was added 5% aqueous Na_2CO_3solution and washed with EtOAc. The aqueous layer was acidified with 5 N HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Synthesis of amide derivatives 42–44: General procedure

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

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

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

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

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

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

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

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

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

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

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

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

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

Synthesis of amines derivatives 14–17: General procedure

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

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

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

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

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

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

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

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

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

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

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

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

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

Attempted preparation of sulfonamide 46

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

Experiment 2: *N*-(2-benzyl-2-methyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl)naphthalene-2-sulfonamide 49 and *N*-benzyl-*N*-(2-methyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl)naphthalene-2-sulfonamide 50. To a stirred solution of indanone sulfonamide **28** (1.0 g, 2.85 mmol) in dry THF (15 mL) cooled to −78 °C was added *via* a hypodermic syringe LDA mono-THF complex solution (1.5 M in cyclohexane, 6.7 mL, 9.98 mmol) under argon atmosphere. After stirring at −78 °C for 1 h, the slurry was allowed to warm to room temperature for 4 h. The resulting dark red solution was cooled to −40 °C and a solution of benzyl bromide (0.85 mL, 7.13 mmol) in dry THF (10 mL) was added. The resultant mixture was stirred at room temperature for 18 h. The reaction mixture was quenched by addition of brine (20 mL) and 2.5 N HCl (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (hexanes–EtOAc mixtures of increasing polarity as eluent) to afford the benzylindanone derivatives **49** (660 mg, 52%) and **50** (160 mg, 11%) as off-white solids.

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

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

5-HT_6 binding assay

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

Adenylyl cyclase activity assay

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

Acknowledgements

This research was supported by ESTEVE, Barcelona, Spain, through projects FBG-301362, FBG-302131 and FBG-302663 Fundació Bosch i Gimpera-Universitat de Barcelona, Spain. N.M. and S.L.-P. are grateful to ESTEVE for post-doctoral and graduate fellowships, respectively. Thanks are also due to the AGAUR, *Grup de Recerca Consolidat* 2005SGR00158.

References

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

