Discovery of *N*-[(2*S*)-5-(6-fluoro-3-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide, a novel clinical AMPA receptor positive modulator

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1. Plasma Protein Binding of 17i in Mouse, Rat, Dog, Cynomolgus Monkey and Human. The in vitro plasma protein binding of **17i** was determined using equilibrium dialysis. Dialysis membrane strips were soaked in water for 1 h, and then in a 20% ethanol solution for a minimum of 20 min. The membrane strips were twice washed in water and then compressed between the Teflon strips containing half wells to form a 96-well format plate. Phosphate buffer (pH7.4) was immediately added to the bottom half of each well.

17i (1 µg/mL) in plasma from mouse, rat, dog, monkey and human was added to the top half of a well (n = 12 per species). The attainment of dialysis equilibrium was assessed by dialysing control buffer against spiked buffer (n = 12). The plate was equilibrated for 6 h on a plate shaker at approximately 37 °C. An aliquot (50 µL) of each half well was withdrawn and diluted with an equal volume of the opposite matrix. An aliquot of the original spiked plasma (undialysed) was also analysed to investigate the recovery obtained. Samples were mixed on a plate shaker for a minimum of 5 min and then stored in a fridge overnight prior to analysis. The samples were prepared by protein precipitation prior to analysis by LCMSMS.

The response ratio for each dialysed plasma and buffer sample and the mean value of the spiked plasma sample was used to calculate the recovery using the following equation:

$$\frac{response\ ratio\ of\ the\ dialysed\ \ plasma\ sample + response\ ratio\ of\ the\ dialysed\ buffer\ sample}{mean\ response\ ratio\ of\ the\ undialysed\ spiked\ \ plasma\ sample} \times 100$$

The response ratio for both the top and bottom halves of the spiked buffer samples were used to calculate the equilibrium ratio using the following equation:

$$\frac{response\ ratio\ of\ \ the\ bottom\ half\ \ of\ \ the\ spiked\ buffer\ well}{response\ ratio\ of\ \ the\ top\ half\ \ of\ \ the\ spiked\ buffer\ well}$$

Plasma protein binding was calculated using the following equation:

$$\%\ \text{bound} = \frac{(x - y)}{x} \times 100$$

Where:

x = peak area of **17i** in plasma compartment after 6 h dialysis relative to IS
y = peak area of **17i** in buffer compartment after 6 h dialysis relative to IS

2. Brain Tissue Binding of 17i in the Rat. The *in vitro* brain tissue binding of **17i** was determined using equilibrium dialysis. Dialysis membrane strips were soaked in water for 1 h, and then in a 20% ethanol solution for a minimum of 20 min. The membrane strips were twice washed in water and then compressed between the Teflon strips containing half wells to form a 96-well format plate. Phosphate buffer (150µL, pH7.4) was immediately added to the bottom half of each well.

Aliquots (150 µL) of 17i (1 µg/mL) in brain homogenate (1g brain homogenate:2 mL phosphate buffer) were added to the top half of a well (n = 3). The plate was equilibrated for 6 h on a plate shaker at approximately 37 °C. An aliquot of 50 µL of brain homogenate was removed from the top half of the well and diluted with 100 µL of buffer and 100 µL of buffer was withdrawn from the lower half of the well and diluted with 50 µL of brain homogenate. Samples were mixed on a plate shaker for a minimum of 5 min and then stored at approximately 4 °C prior to analysis. The samples were prepared

by protein precipitation prior to analysis. The peak area of **17i** in the brain compartment after 6 h dialysis relative to the IS was determined using HPLC-MS/MS

Calculation of Fraction Unbound (Fu)

For each aliquot the peak area ratio of 17i to internal standard (I.S. ratio) was calculated.

This ratio was then used to calculate the measured fraction unbound (*fu*):

$$fu\ measured = \frac{I.S.ratio[Buffer]}{I.S.ratio[Tissue]}$$

fu measured was then adjusted for the 1:3 dilution of brain tissue as follows:

$$undiluted\ fu\ measured = \frac{(1/D)}{((1/\ fu\ measured) - 1)} + (1/D)$$

D = Dilution factor = 3

Calculation of % Binding

The degree of **17i** binding to homogenised brain tissue was calculated from the following equation:

$$\%binding = \left(1 - undiluted\ fu\right).100\right)$$

3. Membrane permeability, P-glycoprotein transport and interaction. The potential for human P-glycoprotein (P-gp) to transport **17i** was investigated using Madin-Darby Canine - MultiDrug-Resistant (MDCKII-MDR1) cells heterogeneously expressing human P-gp. Directional transport rates of **17i** (0.5 μM) were measured in the absence and presence of a potent P-gp inhibitor, GF120918 (2 μM), to confirm the role of P-gp in the transport of **17i**, and to determine the passive membrane permeability of **17i**. The apical efflux ratios of **17i** were 1.1, both in the absence and presence of the P-gp inhibitor, suggesting that **17i** was not a substrate of human P-gp. The passive membrane permeability of **17i** in

MDCKII-MDR1 cells was high (from 449 to 482 nm/sec).

4. *In vivo* studies. All experiments were performed in accordance with the United Kingdom Animals (Scientific Procedures) Act, 1986 under Project Licence as well as under the review and approval of the GlaxoSmithKline Procedures Review Panel. GlaxoSmithKline safety regulations were adhered to at all times.

5. Analysis of blood, plasma or brain samples from *in vivo* and protein binding studies

All samples were prepared in accordance with internal guidelines.

Blood, dialysed plasma, dialysed buffer and dialysed brain homogenate. Samples (50, 100 or 150µL) were extracted by protein precipitation with extraction buffer (95:5 acetonitrile:ethanol with 0.1% (v/v) formic acid) containing a suitable internal standard . Samples were assayed for 17i concentrations using HPLC-MS/MS

*Brain***.** Each brain was diluted with 2.15 mL of methanol:water (1:1) per gram of brain and homogenised. An aliquot of each brain homogenate was extracted by protein precipitation extraction buffer (95:5 acetonitrile:ethanol with 0.1% (v/v) formic acid) containing a suitable internal standard . Samples were assayed for 17i concentrations using HPLC-MS/MS

*Pharmacokinetic Analysis of Data for **17i**.* For *in vivo* pharmacokinetic studies, non-compartmental parameters were derived from the blood concentration-time profiles using PKTools (Version 2.0).

For brain penetration studies, the ratio of the area under the brain and blood concentration-time curve (AUC) were compared to give estimates of the brain:blood ratio.

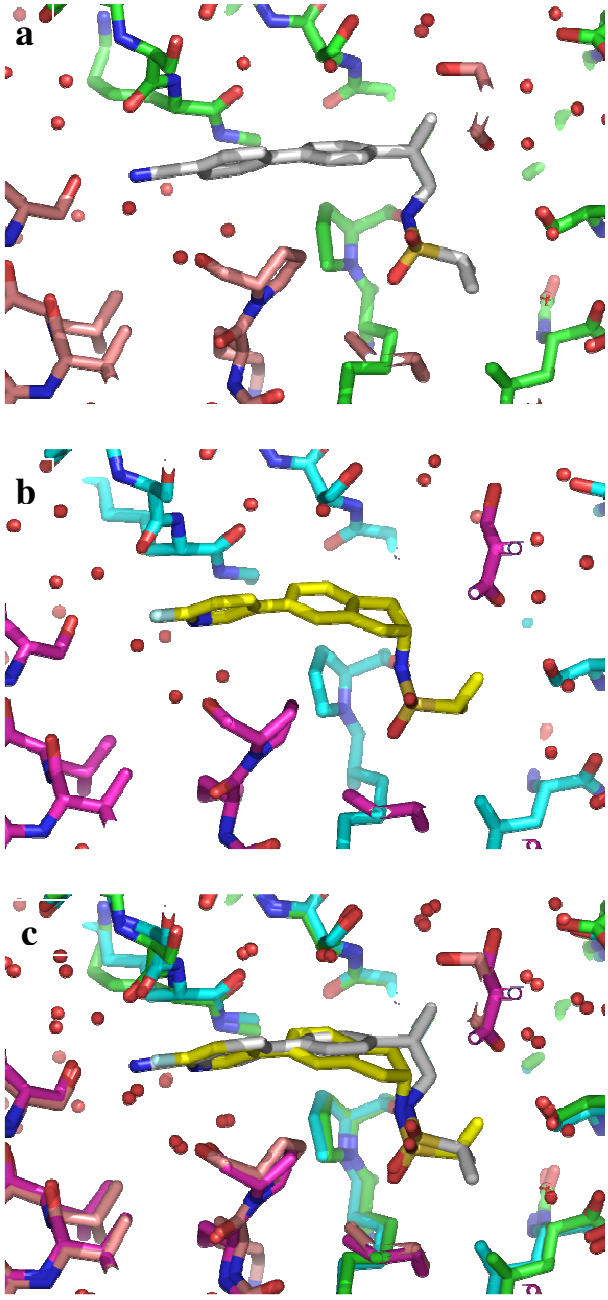
6. High resolution Mass Spectrometry methods. Positive ion mass spectra were acquired as accurate mass centroided data using a Micromass Q-Tof 2 hybrid quadrupole time-of-flight mass spectrometer, equipped with a Z-spray interface, over a mass range of 80 – 1100 Da, with a scan time of 0.95 s and an interscan delay of 0.07 s. Reserpine was used as the external mass calibrant ($[M+H]^+$ = 609.2812 Da). The Q-Tof 2 mass spectrometer was operated in W reflectron mode to give a resolution (FWHM) of 16000-20000. Ionization was achieved with a spray voltage of 3 kV, a cone voltage of

30V, with cone and desolvation gas flows of 5-10 and 500 L/min respectively. The source block and desolvation temperatures were maintained at 120°C and 250°C respectively. The elemental composition was calculated using MassLynx v3.5 for the $[M+H]^+$ and the mass error quoted as ppm.

*Chromatography and analysis for **11a*****:** An Agilent 1100 Liquid Chromatograph equipped with a model G1367A autosampler, a model G1312A binary pump and a HP1100 model G1315B diode array detector was used. The method used was generic for all experiments. All separations were achieved using a Phenomenex Luna C18(2) reversed phase column (150 x 2.1 mm, 3µm particle size). Gradient elution was carried out with the mobile phases as (A) water containing 0.1% (v/v) formic acid and (B) acetonitrile containing 0.1% (v/v) formic acid. The conditions for the gradient elution were initially 0% B, increasing linearly to 100% B over 21 minutes, remaining at 100% B for 5 minutes then decreasing linearly to 0% B over 1 minute followed by an equilibration period of 3 minutes prior to the next injection. The flow rate was 0.4 mL/min, temperature controlled at 25°C with an injection volume of 5 µL. All samples were diluted 1:10 in DMSO (99.9%) prior to LC/MS analysis.

Chromatography and analysis for all other compounds: An Agilent 1100 Liquid Chromatograph equipped with a model G1367A autosampler, a model G1312A binary pump and a HP1100 model G1315B diode array detector was used. The method used was generic for all experiments. All separations were achieved using a Phenomenex Luna C18(2) reversed phase column (150 x 2.1 mm, 3µm particle size). Gradient elution was carried out with the mobile phases as (A) water containing 0.1% (v/v) formic acid and (B) acetonitrile containing 0.1% (v/v) formic acid. The conditions for the gradient elution were initially 0% B, increasing linearly to 100% B over 21 minutes, remaining at 100% B for 5 minutes then decreasing linearly to 0% B over 1 minute followed by an equilibration period of 3 minutes prior to the next injection. The flow rate was 0.4 mL/min, temperature controlled at 25°C with an injection volume of 5 µL. All samples were diluted 1:10 in DMSO (99.9%) prior to LC/MS analysis.

7. Comparison of the crystal structure of LY 404187 and 17i



Supplementary. Figure 1. Comparison of: a) the crystal structure of LY 404187 with rat GluA12 S1S2 LBD (pdb code: 3KGC)[1] and b) **17i** in human GluS121 S1S2 LBD. In c the structures are shown superposed.

Table 1 Data collection and Refinement Statistics	
Space Group	$P2_12_12$
Unit Cell Dimensions: (Å)	
a	99.14
b	121.78

c	47.49
Resolution Range (Å) (last Shell)	40-1.80 (1.83-1.80)
Unique Reflections	53509
Redundancy	4.3
I/σ(I) overall (last shell)	18.4 (3.6)
Completeness (%) (last shell)	99.4 (100.0)
Rmerge (%) (last Shell)	7.3 (39.0)
Data Range for Refinement (Å) (last shell)	20-1.80 (1.85-1.80)
Rwork (%) (last shell)	19.8 (24.7)
Rfree (%) (last shell)*	23.6 (27.9)
RMSd	
Bonds (Å)	0.017
Angles (°)	1.17

8. Experimental details for preparation of molecules not already provided in main paper

3-(2-x-2,3-dihydro-1*H*-inden-5-yl)-*N*,*N*-dimethylbenzenesulfonamide (11b): yield 36%. MS (ES-) *m/z* 421 (M – 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (6H, d, *J* = 7 Hz), 2.75 (6H, s), 2.99 (2H, m), 3.21 (1H, m), 3.38 (2H, m), 4.37 (2H, m), 7.32 (1H, d, *J* = 8 Hz), 7.43 (2H, m), 7.60 (1H, m), 7.76 (2H, m), 7.95 (1H, m).

***N*-[5-(3-acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-propanesulfonamide (11d):** yield 11%. MS (ES+) *m/z* 358 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.42 (6H, d, *J* = 7 Hz), 2.66 (3H, s), 2.99 (2H, m), 3.20 (1H, m), 3.35 (2H, m), 4.29 (2H, m), 7.32 (1H, m), 7.46 (2H, m), 7.56 (1H, m), 7.76 (1H, m), 7.92 (1H, m), 8.14 (1H, m).

***N*-{5-[3-(2-oxopropyl)phenyl]-2,3-dihydro-1*H*-inden-2-yl}-2-propanesulfonamide (11e):** yield 7%. MS (ES-) *m/z* 370 (M – 1). ^{1}H-NMR (400 MHz, CDCl3): 1.40 (6H, m), 2.20 (3H, s), 2.96 (2H,

m), 3.20 (1H, m), 3.36 (2H, m), 3.76 (2H, s), 4.34 (1H, m), 4.46 (1H, m), 7.18 (1H, m), 7.26 (2H, m), 7.43 (4H, m).

***N*-[3-(2-{[(1-methylethyl)sulfonyl]amino}-2,3-dihydro-1H-inden-5-yl)phenyl]acetamide (11f):** yield 48%. MS (ES+) *m/z* 373 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (6H, d, *J* = 7 Hz), 2.20 (3H, s), 2.96 (2H, m), 3.20 (1H, m), 3.34 (2H, m), 4.33 (1H, m), 4.41 (1H, m), 7.23 (2H, m), 7.38 (5H, m), 7.74 (1H, m).

***N*-[5-(3-nitrophenyl)-2,3-dihydro-1H-inden-2-yl]-2-propanesulfonamide (11g):** yield 7%. MS (ES-) *m/z* 421 (M – 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (6H, d, *J* = 7 Hz), 2.88 (3H, s), 2.97 (2H, m), 3.20 (1H, m), 3.37 (5H, m), 4.32 (2H, m), 7.30 (3H, m), 7.45 (4H, m).

***N*-[5-(3-aminophenyl)-2,3-dihydro-1H-inden-2-yl]-2-propanesulfonamide (12).** A solution of molecule **11g** (430 mg, 1.19 mmol) in ethanol (10 mL) was treated with 10% palladium on charcoal (paste) (100mg), and then stirred under an atmosphere of hydrogen at room temperature and pressure for 24 h. The mixture was filtered through a bed of kieselguhr and washed through with ethanol. The filtrate was removed under reduced pressure to give the title compound as a colourless solid (320 mg, 81%). MS (ES-) *m/z* 329 (M – 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.36 (6H, m), 2.94 (2H, m), 3.17 (1H, m), 3.35 (2H, m), 3.77 (2H, bs), 4.31 (2H ,m), 6.67 (1H, m), 6.87 (1H, m), 6.95 (1H, m), 7.22 (2H, m), 7.39 (2H, m).

General procedure for preparation of 13a-c. A mixture of *N*-[5-(3-aminophenyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (**12**) (0.30 mmol), and diisopropylethylamine (0.61 mmol), in dry dimethylformamide (2 mL) was treated with appropriate sulfonyl or acetyl chloride (0.30 mmol) and stirred at room temperature for 1h. Sodium hydride (60% dispersion in oil, 0.38 mmol) was added and the mixture stirred at 60 °C for 0.5 h. The reaction mixture was cooled then partitioned between dichloromethane and 0.5 M hydrochloric acid, and the organic layer was evaporated under reduced pressure and purified by column chromatography.

2-Methyl-*N*-[3-(2-{[(1-methylethyl)sulfonyl]amino}-2,3-dihydro-1H-inden-5-

yl)phenyl]propanamide (13a): yield 79%. MS (API+) *m/z* 399 (M - 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.28 (6H, m), 1.41 (6H, d, *J* = 7 Hz), 2.54 (1H, m), 2.96 (2H, m), 3.20 (1H, m), 3.36 (2H, m), 4.34 (2H, m), 7.28 (3H, m), 7.37 (4H, m), 7.85 (1H, m).

***N*-(5-{3-[(ethylsulfonyl)amino]phenyl}-2,3-dihydro-1H-inden-2-yl)-2-propanesulfonamide (13b):** yield 63%. MS (API) *m/z* 421 (M – 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.42 (9H, m), 2.98 (2H, m), 3.18 (3H, m), 3.37 (2H, m), 4.36 (2H, m), 7.21 (2H, m), 7.29 (1H, m), 7.39 (4H, m).

***N*-{5-[3-(1,1-dioxido-2-isothiazolidinyl)phenyl]-2,3-dihydro-1*H*-inden-2-yl}-2-propanesulfonamide (13c):** yield 9%. MS (ES-) *m/z* 433 (M – 1); ^{1}H-NMR (400 MHz, CDCl3): 1.41 (6H, d, *J* = 7 Hz,), 2.56 (2H, m), 2.95 (2H, m), 3.20 (1H, m), 3.36 (2H, m), 3.41 (2H, t, *J* = 8 Hz), 3.84 (2H, m), 4.32 (2H, m), 7.23 (1H, m), 7.27 (1H, m), 7.32 (1H, m), 7.39 (4H, m). HRMS (ES+) *m/z* 435.1412 ($[M + H]^+$ calcd for $C_{21}H_{22}N_2O_4S_2^+$ 435.1412).

***N*-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (16).** A mixture of (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) chloride complex with dichloromethane (3 mol%, 200 mg, 0.27 mmol), potassium acetate (2.64 g, 26.9 mmol), and bis(pinacolato)diboron (2.3 g, 9.1 mmol) in dimethylsulfoxide (60 mL) was degassed with argon for 5 min. A solution of **10** (3.0 g, 8.22 mmol) in dimethylsulfoxide (20 mL) was added and the resulting mixture stirred at 80 °C under argon for 3 h. The reaction mixture was allowed to cool and diluted with ethyl acetate. This solution was washed three times with water. The organic layer was separated, dried over sodium sulfate and evaporated under reduced pressure to give a dark oil (3.25 g) which was purified by chromatography on a 50 g Isolute™ Flash silica-gel column, eluting from 0-50% ethyl acetate in petroleum ether to give the title compound as a brown oil (2.60 g, 87%). MS (API-) *m/z* 364 (M - 1); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.34 (12H, s), 1.39 (6H, d, *J* = 7 Hz), 2.90 (2H, m), 3.18 (1H, m), 3.32 (2H, m), 4.27 (2H, m), 7.26 (1H, m), 7.65 (2H, m).

General procedure for Suzuki coupling from 10 to prepare 17a-c. A mixture of **10** (0.18 mmol) and caesium carbonate (0.27 mmol) in a 3:1 mixture of 1,4-dioxan:water (4 mL) was degassed with

argon for 5 min. Then the mixture was added to a pyridyl boronic acid (0.20mmol). Palladium acetate (0.01 mmol - alternatively, solid supported palladium may be used), and triphenylphosphine (0.03 mmol) were then added and the whole mixture stirred at reflux for 16 h. The reaction mixture was allowed to cool and partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, dried and evaporated. The resulting product was purified using mass directed preparative HPLC to give the title compound.

***N*-[5-(3-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (17a):** yield 45%. MS (API+) *m/z* 317 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.40 (6H, d, *J* = 7 Hz), 3.00 (2H, m), 3.21 (1H, m), 3.37 (2H, m), 4.34 (1H, m), 5.04 (1H, m), 3.32 (1H, m), 7.41 (3H, m), 7.91 (1H, m), 8.57 (1H, m), 8.75 (1H, m).

***N*-[5-(2-fluoro-3-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (17b):** yield 37%. MS (API+) *m/z* 335 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.41 (6H, d, *J* = 7 Hz), 2.98 (2H, m), 3.21 (1H, m), 3.38 (2H, m), 4.35 (2H, m), 7.38 (3H, m), 7.66 (1H, m), 7.84 (1H, m), 8.19 (1H, m).

***N*-[5-(6-fluoro-3-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (17c):** yield 31%. MS (API+) *m/z* 335 (M + 1); ^{1}H-NMR (250MHz, $CDCl_3$): δ 1.41 (6H, d, *J* = 7 Hz), 2.98 (2H, m), 3.21 (1H, m), 3.38 (2H, m), 4.40 (2H, m), 7.00 (1H, m), 7.32 (3H, m), 7.93 (1H, m), 8.37 (1H, m).

General procedure for Suzuki coupling from 16 to prepare 17d-g and 18a-d. A mixture of **16** (0.22 mmol), substituted bromo-pyridine (0.22 mmol) and caesium carbonate (0.33 mmol) in a 3:1 mixture of 1,4-dioxan:water (4 mL) was degassed with argon for 5 min. Palladium acetate (0.01 mmol), followed by triphenylphosphine (0.04 mmol) were then added and the whole mixture stirred at 160 °C for 20 min in a microwave reactor. The reaction mixture was allowed to cool and partitioned between ethyl acetate and water. The organic layer was separated and evaporated under reduced pressure. The resulting product was purified on a Flash silica-gel column to give the title compound.

***N*-[5-(2,6-dimethyl-3-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (17d):** yield 52%. MS (API+) *m/z* 345 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (6H, d, *J* = 7 Hz), 2.47 (3H, s),

2.57 (3H, s), 2.96 (2H, m), 3.21 (1H, m), 3.37 (2H, m), 4.37 (2H, m), 7.04 (1H, d, *J* = 8 Hz), 7.13 (2H, m), 7.26 (1H, m), 7.38 (1H, d, *J* = 8 Hz).

***N*-[5-(5-cyano-3-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (17e):** yield 48%. MS (API+) *m/z* 342 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (6H, d, *J* = 7 Hz), 3.00 (2H, m), 3.21 (1H, m), 3.40 (2H, m), 4.35 (1H, m), 4.49 (1H, m), 7.38 (2H, m), 7.42 (1H, m), 8.09 (1H, m), 8.83 (1H, m), 8.97 (1H, m).

***N*-[5-(4-methyl-3-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (17f):** yield 52%. MS (API+) *m/z* 331 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.41 (6H, d, *J* = 7 Hz), 2.73 (3H, s), 2.99 (2H, m), 3.21 (1H, m), 3.38 (2H, m), 4.36 (1H, m), 4.74 (1H, m), 7.12 (1H, dd, *J* = 8 Hz and 1 Hz), 7.17 (2H, m), 7.29 (1H, d, *J* = 8 Hz), 8.30 (1H, s), 8.43 (1H, d, *J* = 5 Hz).

***N*-[5-(6-methyl-3-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (17g):** yield 39%. MS (ES+) *m/z* 331 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (6H, m), 2.60 (3H, s), 2.97 (2H, m), 3.20 (1H, m), 3.38 (2H, m), 4.35 (2H, m), 7.21 (1H, d, *J* = 8 Hz), 7.30 (1H, m), 7.38 (2H, m), 7.73 (1H, dd, *J* = 8 Hz & 2 Hz), 8.68 (1H, d, *J* = 2 Hz).

***N*-[5-(5-fluoro-2-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (18a):** yield 2%. MS (APCI) *m/z* 335 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.40 (6H, m), 2.96 (2H, m), 3.20 (1H, m), 3.38 (2H, m), 4.34 (2H, m), 7.31 (1H, m), 7.47 (1H, m), 7.71 (2H, m), 7.81 (1H, m), 8.52 (1H, m)

***N*-[5-(5-methyl-2-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (18b):** yield 59%. MS (ES+) *m/z* 331 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.39 (6H, m), 2.37 (3H, s), 2.95 (2H, m), 3.24 (1H, m), 3.36 (2H, m), 4.33 (1H, m), 4.41 (1H, m), 7.29 (1H, d, *J* = 8 Hz), 7.57 (2H, m), 7.75 (1H, dd, *J* = 8 Hz & 2 Hz), 7.83 (1H, s), 8.50 (1H, m). HRMS (ES+) *m/z* 331.1466 ($[M + H]^+$ calcd for $C_{18}H_{23}N_2O_2S^+$ 331.1480).

***N*-[5-(3-methyl-2-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (18c):** yield 25%. MS (ES+) *m/z* 331 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (6H, m), 2.34 (3H, s), 2.89 (2H, m), 3.19 (1H, m), 3.33 (2H, m), 4.32 (1H, m), 4.67 (1H, m), 7.18 (1H, m), 7.28 (2H, m), 7.37 (1H, s), 7.58 (1H,

m), 8.53 (1H, m). HRMS (ES+) *m/z* 373.1570 ([M + H]$^+$ calcd for $C_{20}H_{25}N_2O_3S^+$ 373.1586).

***N*-[5-(5-chloro-2-pyridinyl)-2,3-dihydro-1*H*-inden-2-yl]-2-propanesulfonamide (18d):** yield 50%. MS (ES+) *m/z* 351 (M + 1); ^{1}H-NMR (400 MHz, $CDCl_3$): 1.40 (6H, m), 2.96 (2H, m), 3.21 (1H, m), 3.38 (2H, m), 4.33 (2H, m), 7.31 (1H, d, *J* = 8 Hz), 7.64 (1H, m), 7.74 (2H, m), 7.84 (1H, m), 8.62 (1H, m). HRMS (ES+) *m/z* 351.0918 ([M + H]$^+$ calcd for $C_{17}H_{20}N_2O_2SCl^+$ 351.0934).

References

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