Supporting Information

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

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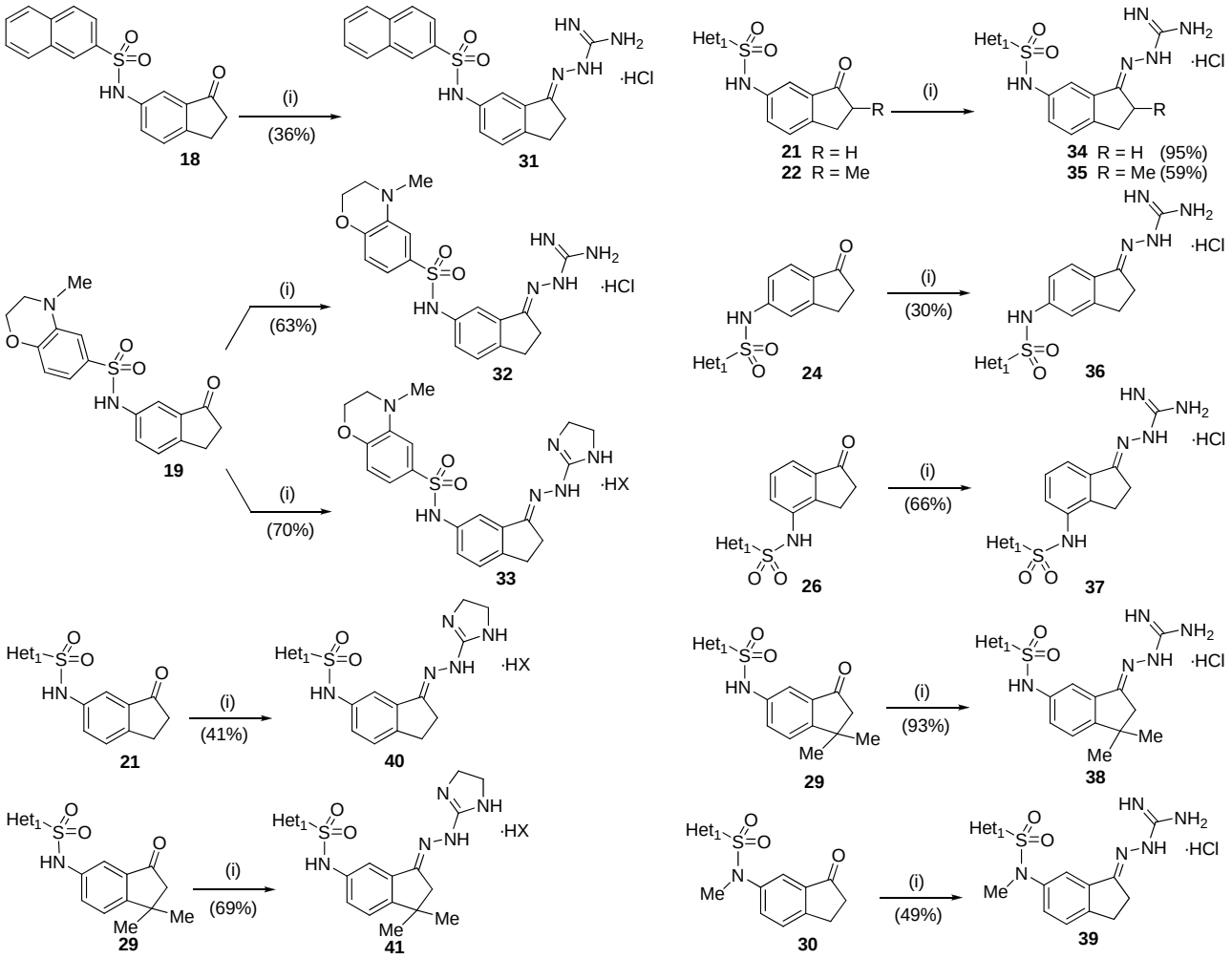
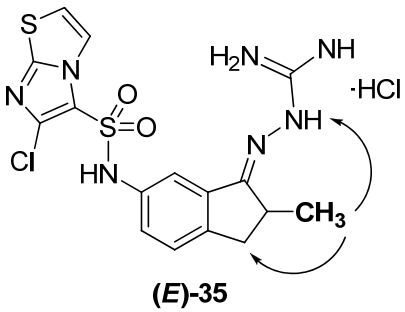


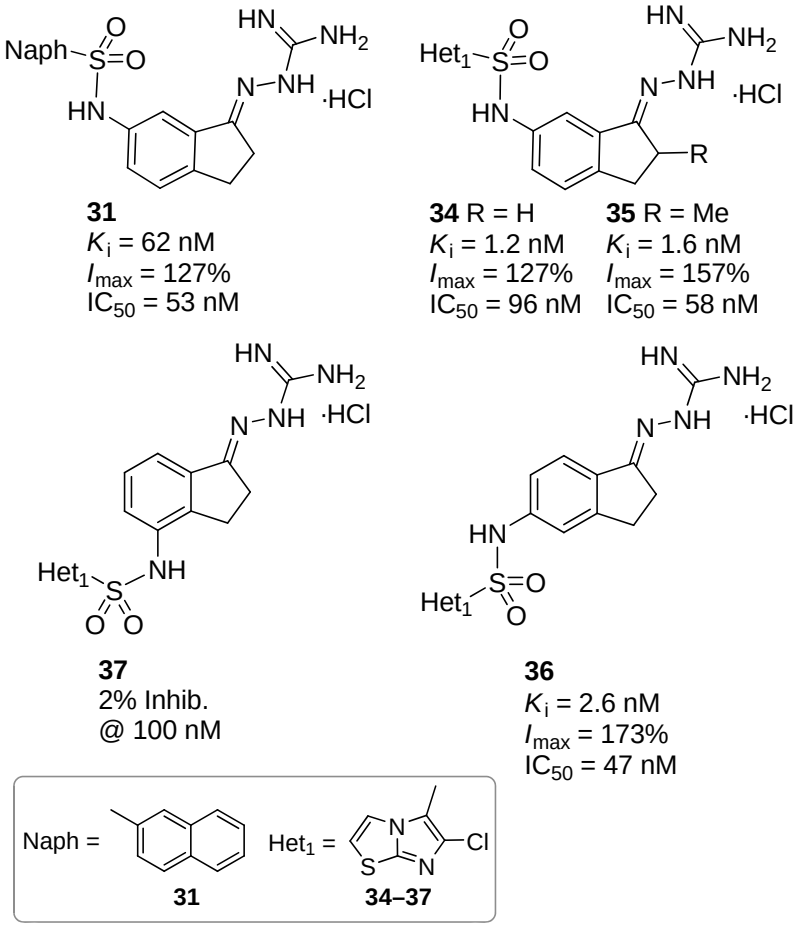
Scheme S1. *Reagents and conditions*: (i) Aminoguanidine hydrogencarbonate or 2-hydrazino-4,5-dihydro-1*H*-imidazole hydrobromide, 37% HCl, solvent, reflux.

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



(*E*)-35

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



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

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

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

37
2% Inhib.
@ 100 nM

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

Naph = **31**

Het_1 = **34–37**

Figure S2

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

Cpd.	Ar(Het)	α_1[b]	α_2[c]	5-HT_{1A}[d]	5-HT_{2c}[d]	SERT[e]
31	Ar_1		$>10^3$	$>10^3$		
32	Ar_2			$>10^3$		
34	Het_1	$>10^3$	$>10^4$	$>10^4$	$>10^4$	$>10^4$
35	Het_1	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$
36	Het_1		$>10^3$	$>10^4$		
38	Het_1		$>10^4$	$>10^3$	$>10^3$	$>10^4$
39	Het_1		$>10^3$	$>10^3$		
40	Het_1	$>10^3$	$>10^4$		$>10^4$	$>10^4$

[a]IC_{50} (nM). [b]Rat α_1-adrenoreceptor. [c]Human α_2-adrenoreceptor. [d]Human receptor. [e]Human transporter.

FULL EXPERIMENTAL SECTION

General Methods

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

Materials

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Synthesis of Indanylsulfonamide guanylhydrazones 31–41. General procedure

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5-HT_6 Binding Assay

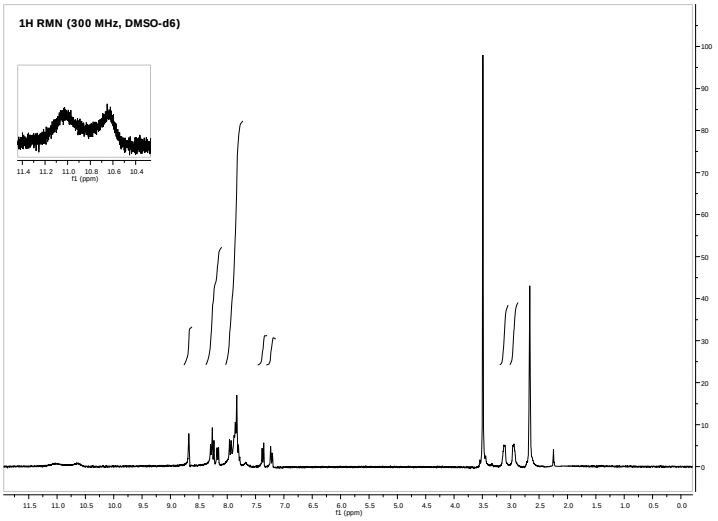
Membranes from HEK-293 with human 5-HT_6 receptor expressed were supplied by Receptor Biology. The binding assays were performed as described by Roth et al.[28a] with slight modifications. The radioligand used was [3H]-LSD at 2.7 nM, and the final volume was 200μL. The incubation was initiated by addition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

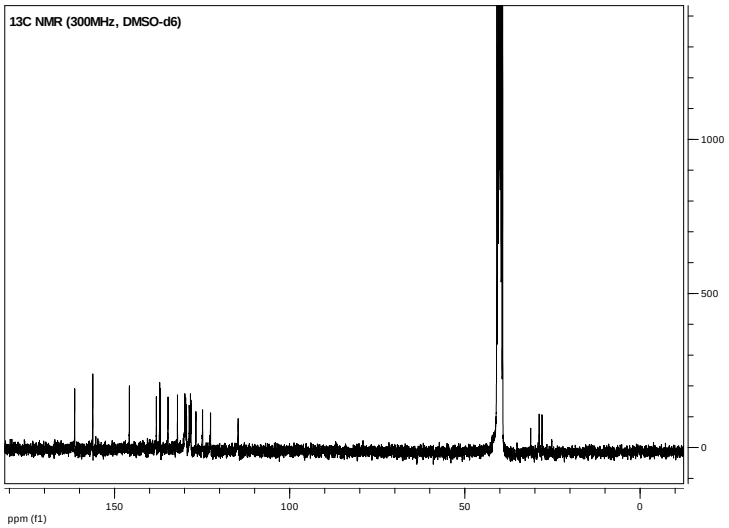
Adenylyl Cyclase Activity Assay

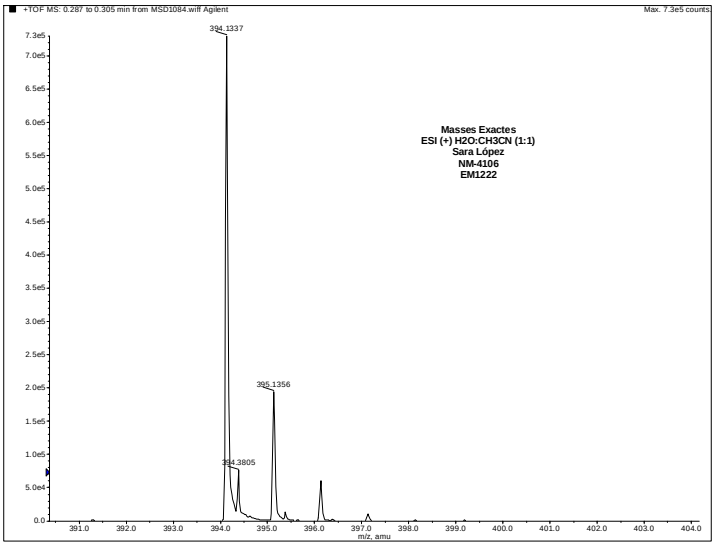
Functional effects of the compounds were evaluated by cAMP measurements on HEK-293F cells stably expressing the human 5-HT_6 receptor using a homogeneous time resolved fluorescence (HTRF) assay format. After overnight serum-free medium incubation, cell suspensión (20,000 cells per well) was added in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

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

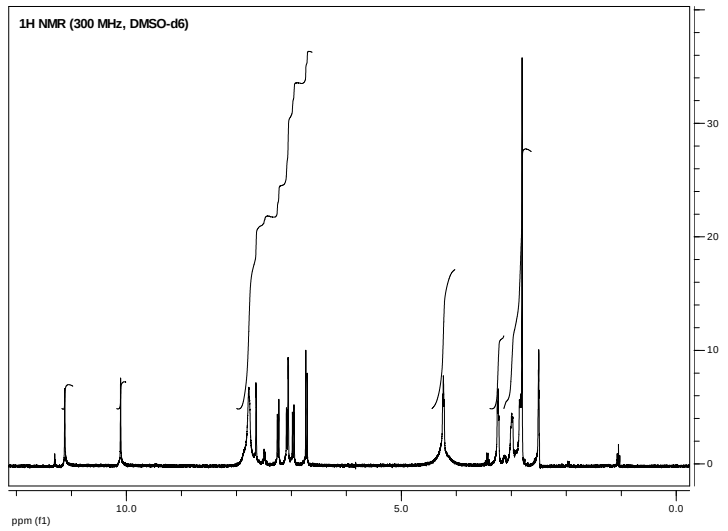
- **2-{6-[(2-Naphthylsulfonyl)amino]-2,3-dihydro-1*H*-inden-1-ylidene}hydrazinecarboximidamide hydrochloride 31**

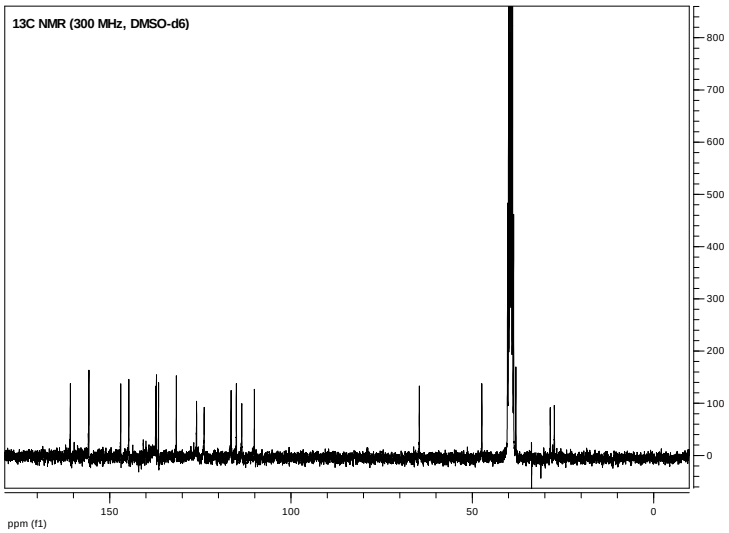


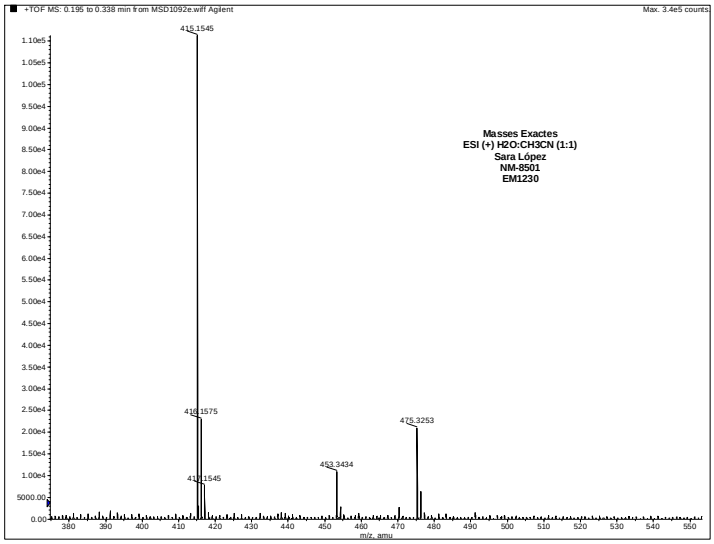




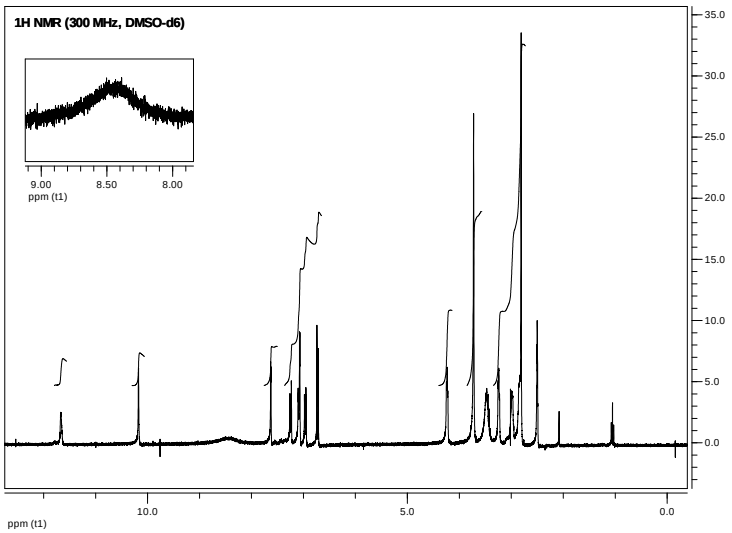
- **2-(6-{[(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-7-yl)sulfonyl]amino}- 2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 32**

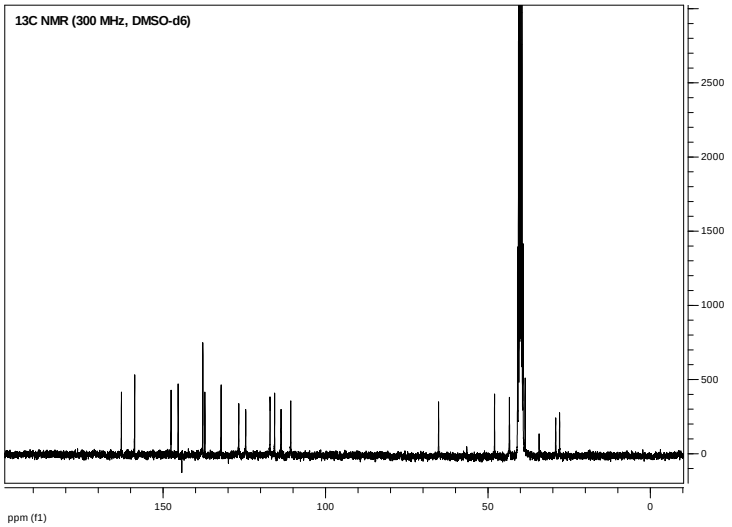


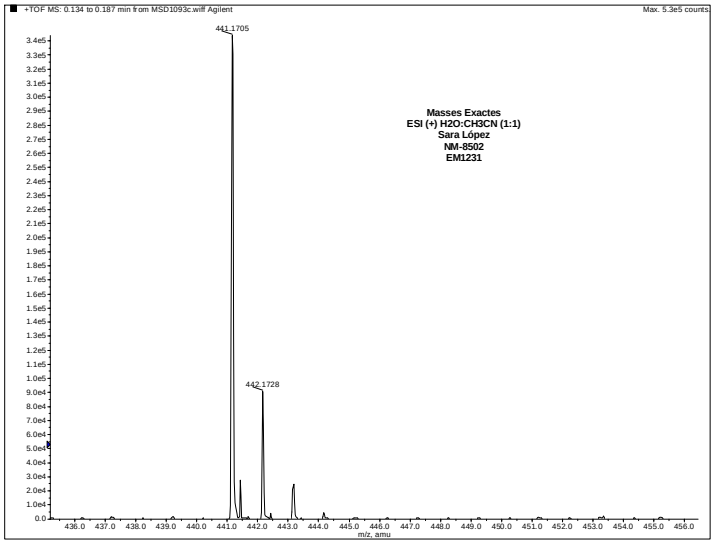




- ***N*-[3-(4,5-dihydro-1*H*-imidazol-2-ylhydrazono-2,3-dihydro-1*H*-inden-5-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-7-sulfonamide hydrohalide 33**

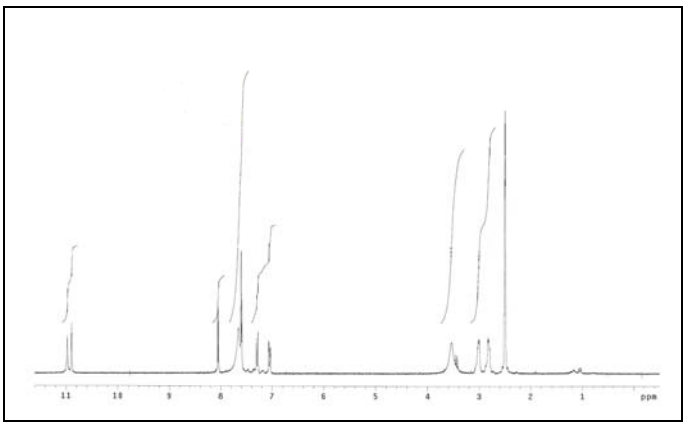




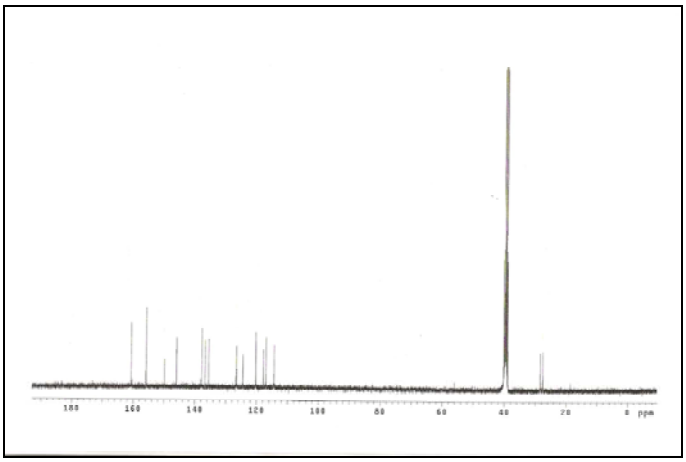


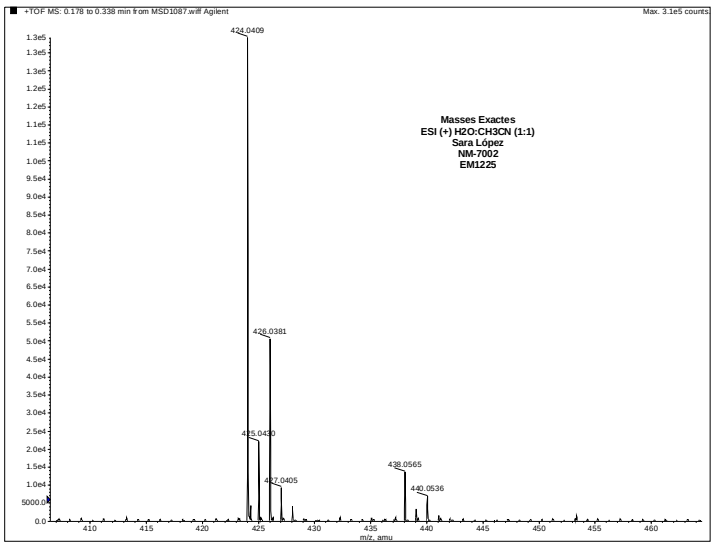
- **2-(6-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 34**

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

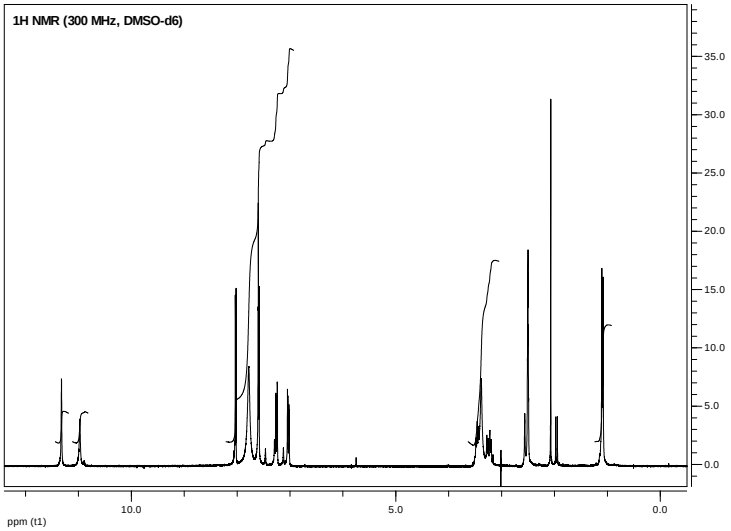


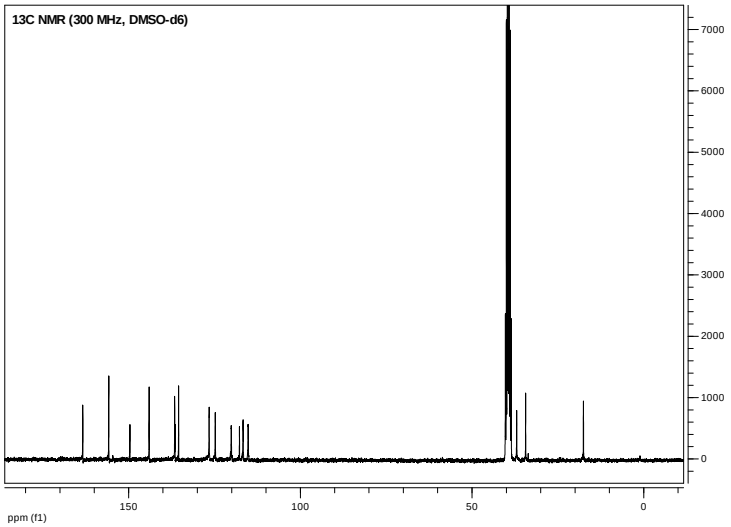
^{13}C NMR (100.6 MHz, DMSO-d_6)

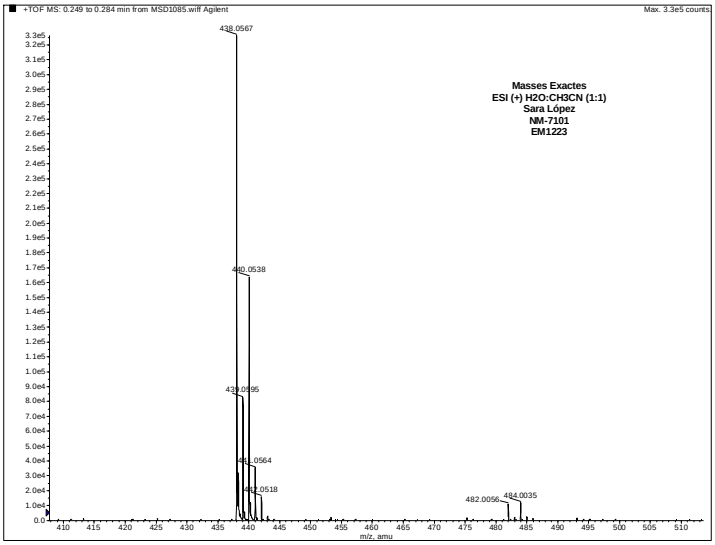




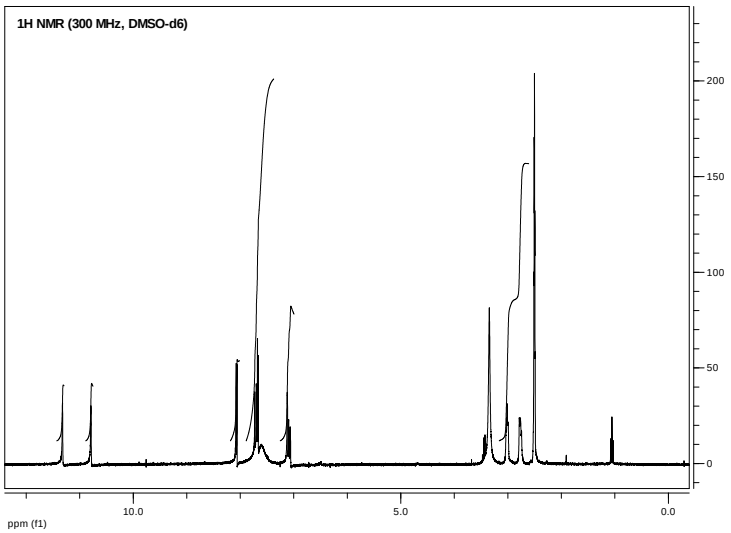
- **2-(6-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2-methyl-2,3-dihydro- 1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 35**

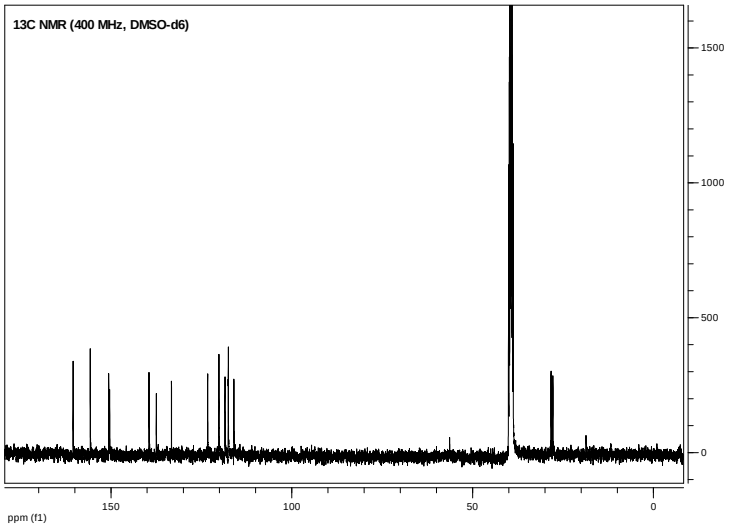


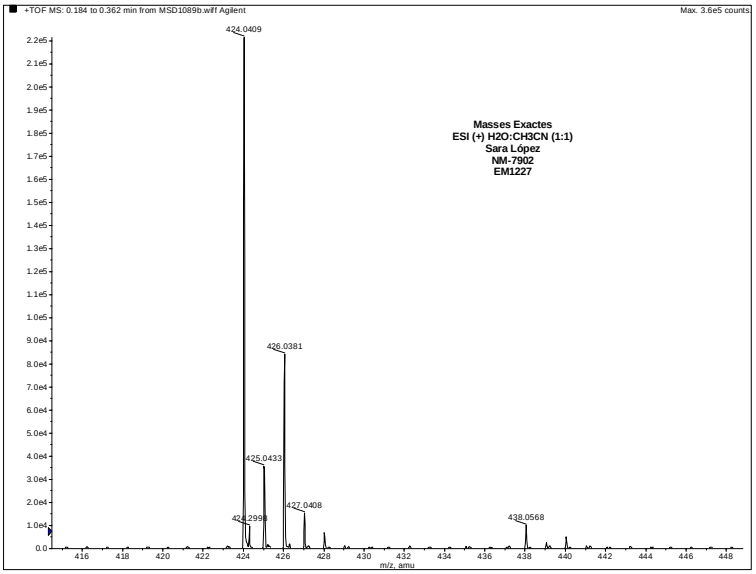




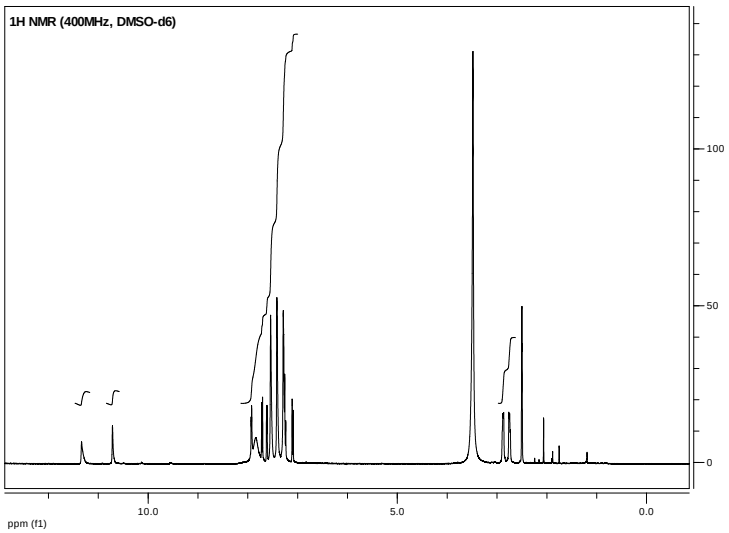
- **2-(5-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 36**

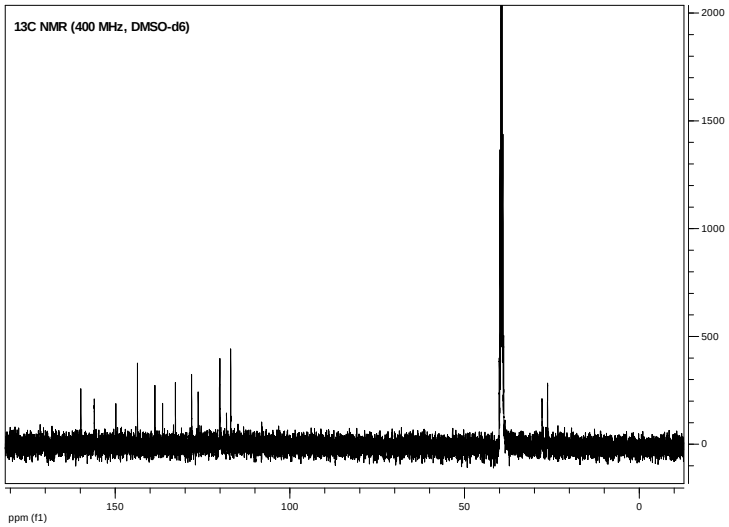


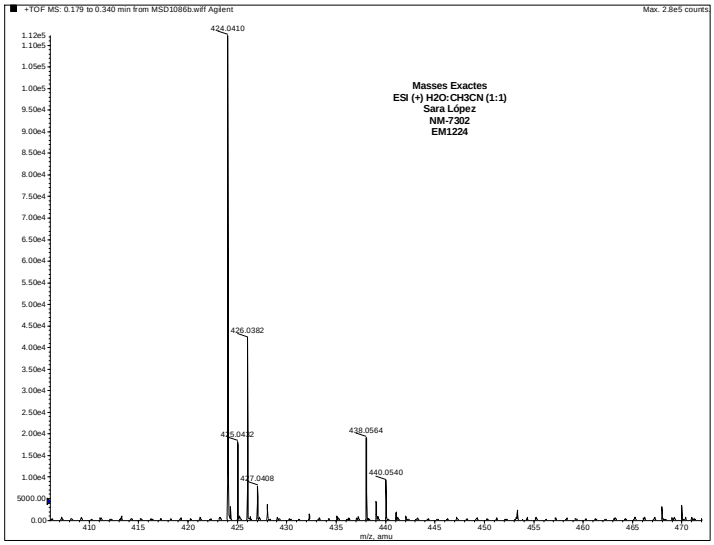




- **2-(4-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-ylidene)hydrazinecarboximidamide hydrochloride 37**

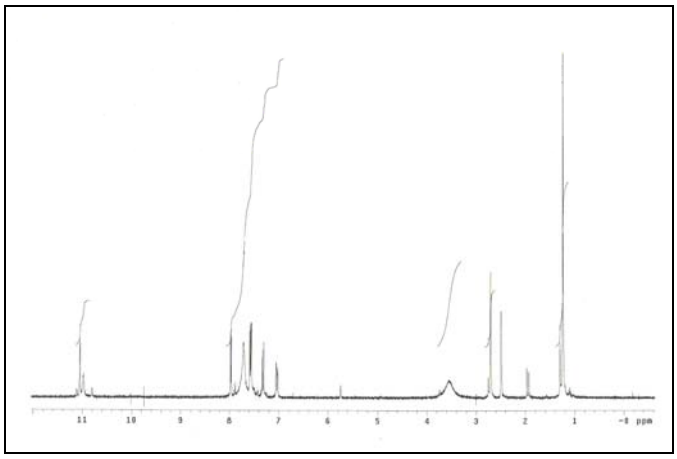


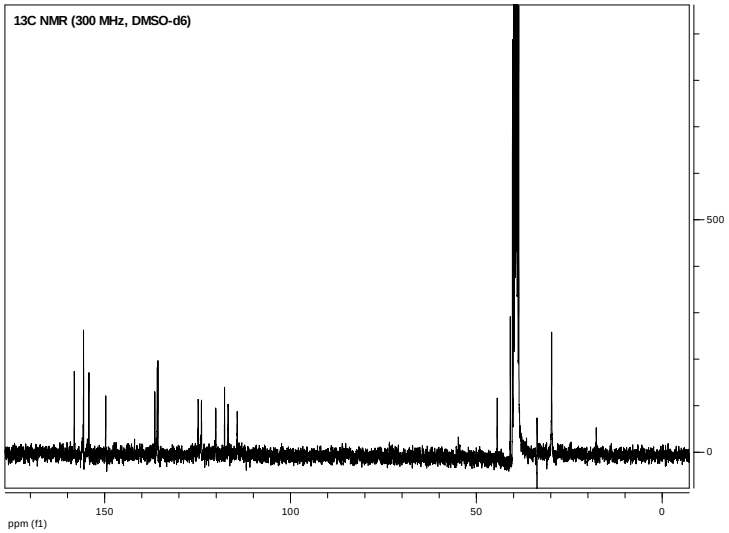


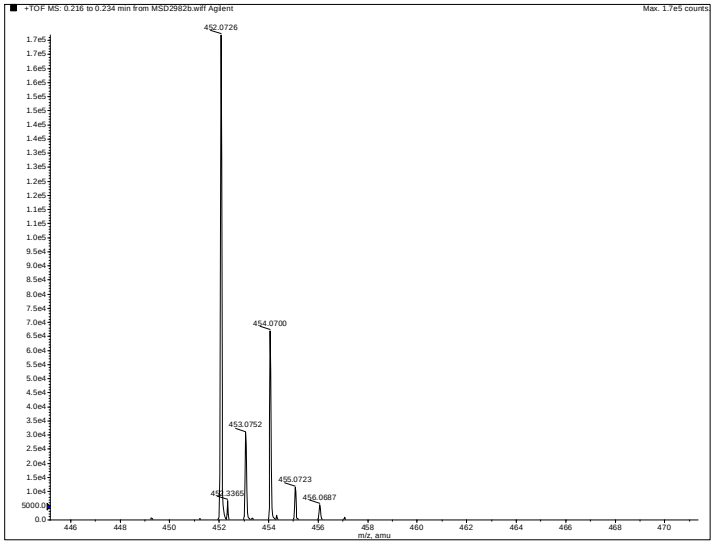


- **2-(6-{[(6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]amino}-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 38**

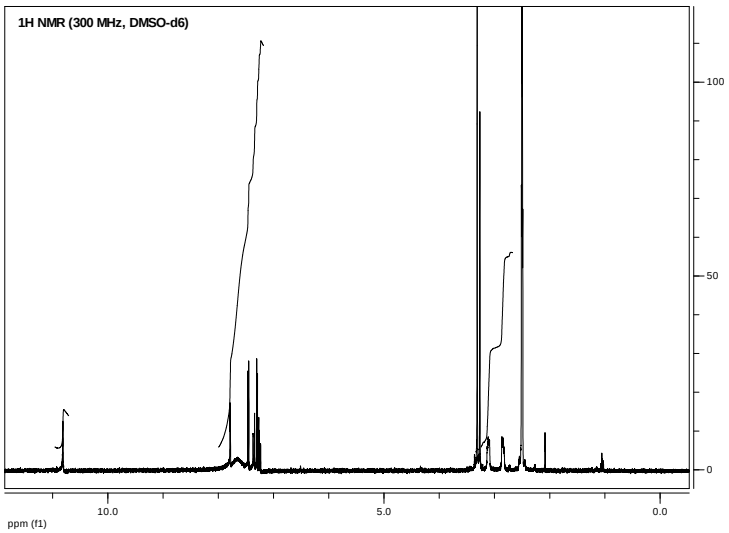
^{1}H NMR (300 MHz, DMSO-d_6)

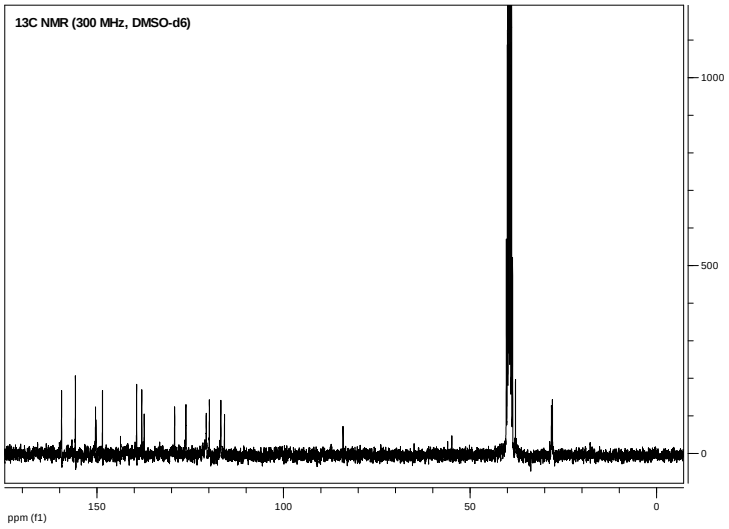


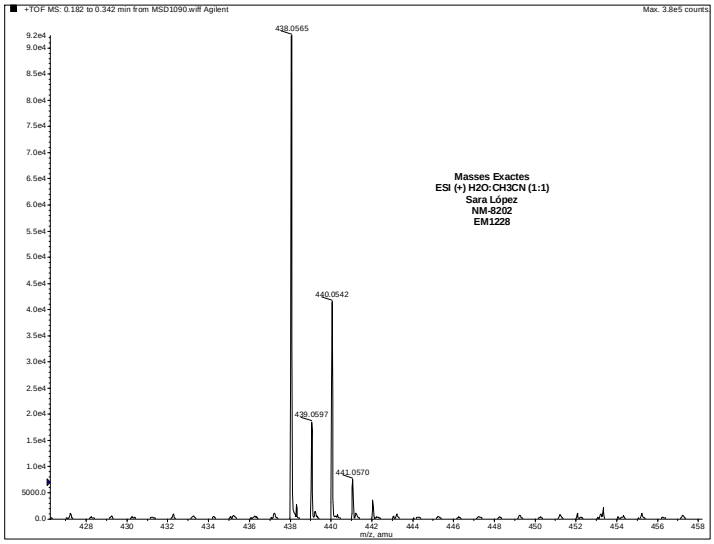




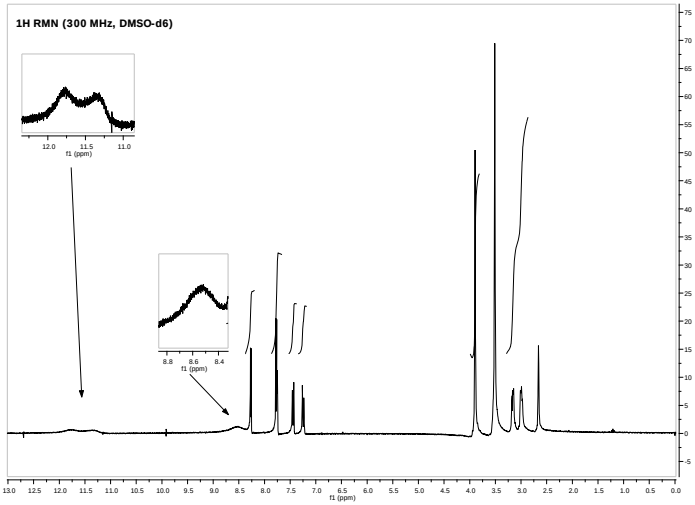
- **2-(6-{[(6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl](methyl)amino}-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboximidamide hydrochloride 39**

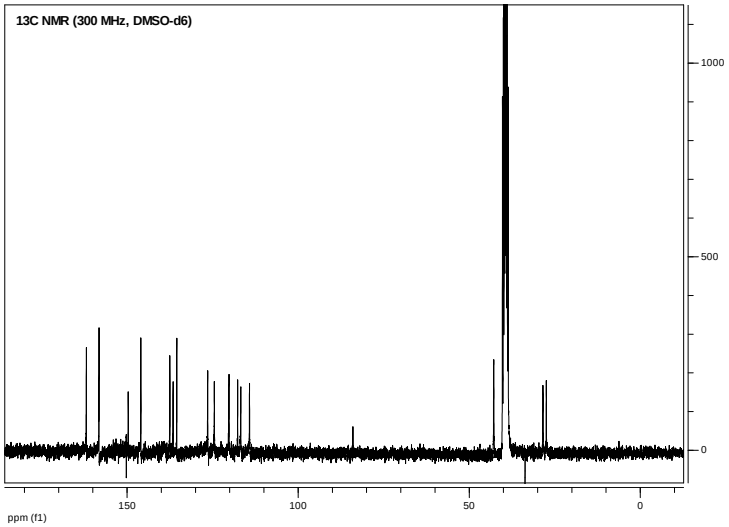


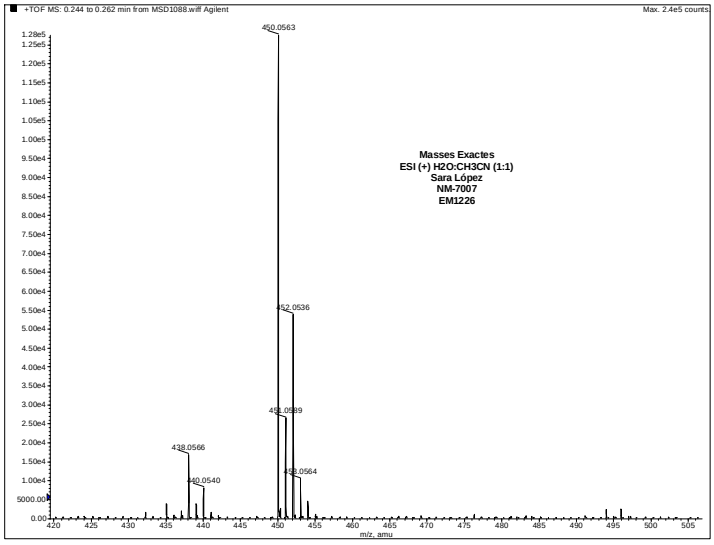




- **6-chloro-*N*-[3-(4,5-dihydro-1*H*-imidazol-2-ylhydrazono)-2,3-dihydro-1*H*-inden-5-yl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide hydrohalide 40**







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