Expedited Articles

Substituted Halogenated Arylsulfonamides: A New Class of σ Receptor Binding Tumor Imaging Agents

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The discovery of a series of novel halogenated arylsulfonamides (HAS) as new σ receptor binding tumor imaging agents is described. Several substituted halogenated sulfonamides have been prepared and characterized. Target compounds were examined for their affinity for σ_1 and σ_2 receptor subtypes using guinea pig brain membranes and rat liver membranes, respectively. A number of substituted halogenated sulfonamides displayed subnanomolar affinities for σ_1 sites and low nanomolar affinities for σ_2 subtype receptors. A limited structure−activity relationship study of this chemical series is discussed. The radioiodination (I-125) of one congener member (4-[^{125}I]iodo-N-[2-(1′-piperidinyl)ethyl]benzenesulfonamide, 4-[^{125}I]IPBS) was accomplished in high yields. The in vitro competition binding studies of 4-[^{125}I]IPBS in guinea pig brain membranes with σ receptor binding ligands confirmed its σ pharmacology. The rank order of potency was BD1008 (*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)-ethylamine) > 4-IPBS > haloperidol > (+)-pentazocine > DTG (1,3-di-*o*-tolylguanidine) > (−)-pentazocine. The inhibition constants (IC_{50}) were 0.70, 1.46, 6.28, 10.4, 87.2, and 152 nM, respectively, and are consistent with labeling of σ_1 receptors. The tumor imaging potential of 4-[^{125}I]IPBS was studied in C57 black mice bearing B16 melanoma xenograft. A high tumor uptake of 4-[^{125}I]IPBS was observed (7.40% ID/g) at 1 h postinjection. The wash out of activity from the tumor was slow at 6 h postinjection (7.22% ID/g). The tumor also had the highest amount of radioactivity (1.54% ID/g) at 24 h postinjection. These results demonstrate that radiohalogenated benzenesulfonamides could be a potentially useful class of compounds in nuclear oncologic scintigraphy.

σ receptor binding ligands consist of a variety of structurally unrelated compounds such as benzomorphans, guanidines, arylethylenediamines, substituted benzamides, phenylpiperidines, and phenylpiperazines.[1−8] On the basis of the opposite enantioselectivity for benzomorphans, different molecular weights, and pharmacological binding studies, two types of σ receptors (σ_1 and σ_2) have been defined.[9] The endogenous σ ligand(s) are not known; however, progesterone has been suggested to be a candidate.[10] The pharmacological significance of σ receptor binding sites remain elusive due to lack of functional and structural information. However, recently the σ_1 binding site, a 30 kDa protein from guinea pig liver, has been purified and cloned. The amino acid sequence of this protein showed no homology to any known mammalian proteins, but a partial homologic resemblance with a fungal protein involved in sterol synthesis was observed.[11]

σ receptors have also been shown to be expressed in a variety of human and rodent tumor cell lines. A very high density of σ_1 and σ_2 receptors is present on human malignant melanoma, breast carcinoma, prostate tumor, and nonsmall cell lung cancer, among other cell lines.[12] The number of σ receptors is found to range between 200000 and about a million receptors/cell, depending upon the nature of the tumor cell line. Furthermore, the in vitro binding experiments from the membrane preparations of human biopsied solid tumors such as brain, breast, and renal carcinomas also revealed a high density of σ receptors as compared to the normal organs.[13−15] σ-receptor binding ligands have also shown the inhibition of proliferation in mammary adenocarcinoma (MCF-7, MDA) and colon carcinoma (LIM l2l5, WIDr) cells as well as melanoma cells and neural tumor cells in culture.[16,17] These results have implicated that σ binding sites may play an important role in cell growth, differentiation, and cell proliferation as well. Furthermore, a recent study using mouse mammary adenocarcinoma cells (line 66) showed the potential of σ receptor binding radioligands as biomarkers of proliferation in breast cancer cells. It was also shown that the density of σ_2 receptors in proliferative cells was about 10-fold higher than quiescent cells.[18] These studies suggested the potential use of σ receptor ligands

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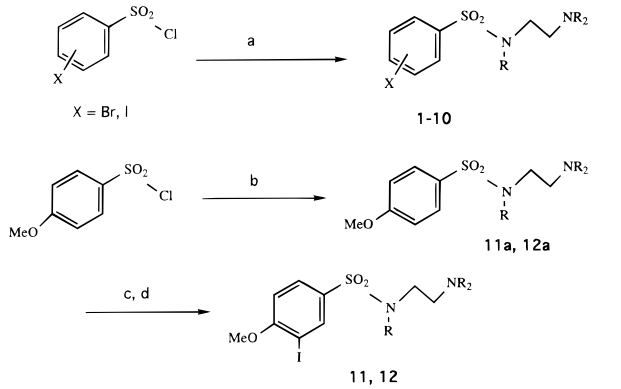
in oncological imaging and in evaluation of proliferating breast tumors.

We have an ongoing research program involving the development of σ receptor binding ligands for noninvasive imaging/therapy of σ receptor positive tumors. Several radioiodinated benzamides have been evaluated for their potential for imaging neoplasms in animal models.[19−21] On the basis of the encouraging preclinical results, several clinical studies have recently been performed in Europe employing radioiodinated benzamides such as *N*-[2-(diethylamino)ethyl]-4-[^{123}I]iodobezamide, 4-[^{123}I]DAB, and *N*-[2-(diethylamino)ethyl]-3-[^{123}I]iodo-4-methoxybenzamide, 3-[^{123}I]MBA, in melanoma patients.[22,23] These patient studies have revealed the fast clearance of radiopharmaceuticals from the blood pool and other nontarget organs that possess σ receptors (such as liver, kidneys, and brain) and a high uptake and retention in tumors. It has been proposed that the uptake of radioiodinated benzamides in melanoma tumors may be related to the melanin content of the melanoma cells. While the mechanism of uptake in melanoma appears controversial, a recent clinical study using 4-[^{123}I]DAB showed a good uptake of tracer in nonsmall cell lung cancer patients as well, probably due to σ receptor binding in human nonsmall cell lung cancer.[24] The number of patient studies has been very few, and extensive clinical trials need to be performed before the clinical use of σ receptor binding radiopharmaceuticals is fully realized. In this study, we report the discovery of halogenated arylsulfonamide (HAS), a new class of high-affinity σ receptor binding ligands. The synthesis, characterization, and pharmacological in vitro binding studies in guinea pig brain membranes and membrane preparations from rat liver, radioiodination of one member of this class of compounds, 4-[^{125}I]iodo-*N*-[2-(1′-piperidinyl)ethyl]benzenesulfonamide, 4-[^{125}I]-IPBS, and its in-vivo tumor imaging potential in a black mouse melanoma tumor model are described.

Chemistry

Several substituted HAS, **1**−**10**, were synthesized by condensation of 1-(2-aminoethyl)pyrrolidine or 1-(2-aminoethyl)piperidine or 1-(2-aminoethyl)homopiperidine or *N*-methyl-2-(1′-homopiperidinyl)ethylamine with 4-bromo- or 4-iodobenzenesulfonyl chloride in the presence of aqueous saturated sodium bicarbonate (Scheme 1). *N*-[2-(1′-Piperidinyl)ethyl]-3-iodo-4-methoxybenzenesulfonamide, **11**, was prepared by condensation of 4-methoxybenzenesulfonyl chloride with 1-(2-aminoethyl)piperidine in the presence of base. The resulting 4-methoxybenzenesulfonamide was then iodinated by an electrophilic thallation procedure using thallium trifluoroacetate−trifluoroacetic acid with molecular iodine. No attempts were made to isolate the resulting intermediate arylthallium ditrifluoroacetate derivative. Some of the halogenated arylsulfonamides were characterized using NMR, mass spectroscopy, and combustion analysis. The results of mass spectroscopy and combustion analyses are summarized in Table 1. To obtain a high yield in radioiodinations and high specific activity of the radioiodinated product, the tri-*n*-butylstannyl precursor, **6a**, was prepared from its corresponding iodo derivative **6** using bis(tri-*n*-butyltin) in the presence of a catalytic amount of tetrakis(tri-

Scheme 1. Synthetic Routes for Substituted Haloarylsulfonamides[a]



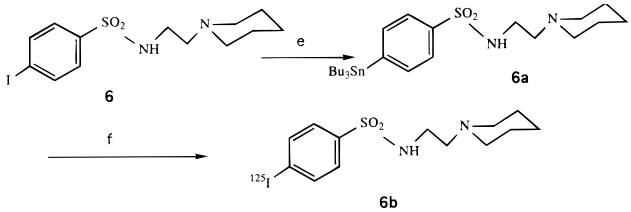
[a] Reagents: (a) *N*,*N*-diethylethylenediamine or 1-(2-aminoethyl)pyrrolidine/piperidine/homopiperidine; (b) 1-(2-aminoethyl)-piperidine or *N*-methyl-2-(1′-homopiperidinyl)ethylamine; (c) $Tl(CO_2CF_3)_3/CF_3COOH$; (d) I_2.

Table 1. Mass Spectroscopic and Combustion Analyses Data for Selected Halogenated Arylsulfonamides

no.	emperical formula	CIMS *m/z* (MH^+)	elemental analysis calcd (found) C	H	N
1	$C_{12}H_{19}N_2SO_2Br$	335	43.00 (42.80)	5.71 (5.83)	8.35 (8.30)
2	$C_{12}H_{19}N_2SO_2I$	383	37.70 (37.71)	5.01 (4.74)	7.33 (7.04)
3	$C_{12}H_{17}N_2SO_2Br$	335	43.25 (43.42)	5.14 (5.17)	8.41 (8.42)
4	$C_{12}H_{17}N_2SO_2I$	381	37.90 (38.05)	4.50 (4.19)	7.30 (7.25)
5	$C_{13}H_{19}N_2SO_2Br$	347	44.96 (44.91)	5.51 (5.56)	8.07 (8.00)
6	$C_{13}H_{19}N_2SO_2I$	395	39.60 (39.86)	4.85 (4.60)	7.10 (7.06)
7	$C_{14}H_{21}N_2SO_2Br$	361	46.54 (46.62)	5.86 (5.77)	7.75 (7.63)
8	$C_{14}H_{21}N_2SO_2I$	409	41.21 (41.47)	5.18 (4.97)	6.80 (6.67)
9	$C_{15}H_{23}N_2SO_2Br$	376	48.00 (47.73)	6.18 (5.94)	7.46 (7.41)
10	$C_{15}H_{23}N_2SO_2I$	423	42.66 (42.44)	5.49 (5.18)	6.63 (6.41)
11	$C_{14}H_{21}N_2SO_3I$	425	38.63 (38.39)	4.99 (4.85)	6.60 (6.28)
12	$C_{16}H_{25}N_2SO_3I$	453	nd[a]		

[a] nd = not determined.

Scheme 2. Preparation of 4-[^{125}I]Iodo-*N*-[2-(1′-piperidinyl)ethyl]benzenesulfonamide, 4-[^{125}I]IPBS[a]



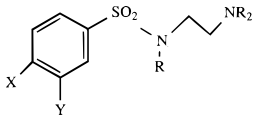
[a] Reagents: (e) $(SnBu_3)_2$, $Pd(PPh_3)_4$, NEt_3; (f) NaI-125, Chloramine-T.

phenylphosphine)palladium(0) in triethylamine. The radioiodination was achieved by an oxidative iododestannylation reaction of 4-(tributylstannyl)benzenesulfonamide, **6a**, and Na^{125}I (carrier free) using chloramine-T as an oxidizing agent (Scheme 2). 4-[^{125}I]Iodo-*N*-[2-(1′-piperidinyl)ethyl]benzenesulfonamide, 4-[^{125}I]IPBS, **6b,** was characterized by HPLC and radio-TLC. The radiolabeled arylsulfonamide was purified using reversed-phase HPLC. The radiochemical yield by solvent extraction was found to range between 89 and 93% (n = 3), and the specific activity was found to be about 1600 Ci/mmol.

Results and Discussion

On the basis of our SAR studies from halogenated benzamides and SAR studies of de Costa et al.[1] on

Table 2. Receptor Binding Data for Halogenated Arylsulfonamides (HAS)[a]



compd	X	R	Y	R_2	K_i (nM) σ_1 guinea pig brain [^{3}H]-(+)-pent	K_i (nM) σ_2 rat liver [^{3}H]DTG
1	Br	H	H	Et_2	10.1 ± 0.3	2826 ± 67
2	I	H	H	Et_2	4.97 ± 0.54	2393 ± 187
3	Br	H	H	$-(CH_2)_4-$	6.65 ± 0.87	1487 ± 26
4	I	H	H	$-(CH_2)_4-$	4.25 ± 0.66	1002 ± 55
5	Br	H	H	$-(CH_2)_5-$	1.54 ± 0.09	459 ± 15
6	I	H	H	$-(CH_2)_5$	0.46 ± 0.07	206 ± 58
7	Br	H	H	$-(CH_2)_6-$	0.63 ± 0.01	198 ± 5.2
8	I	H	H	$-(CH_2)_6-$	1.32 ± 0.93	189 ± 0.8
9	Br	Me	H	$-(CH_2)_6-$	0.18 ± 0.13	44.4 ± 5.6
10	I	Me	H	$-(CH_2)_6-$	0.14 ± 0.03	23.5 ± 1.1
11	OMe	H	I	$-(CH_2)_5-$	41.8 ± 5.6	449 ± 29
12	OMe	Me	I	$-(CH_2)_6-$	3.11 ± 1.6	337 ± 31
haloperidol					3.70 ± 0.6	12.0 ± 1.7
DTG					27.7 ± 4.3	12.8 ± 2.1
(+)-pentazocine					3.1 ± 0.3	1540 ± 313

[a] Twelve concentrations of unlabeled test ligand ranging from 0.05 to 10 000 nM were incubated with guinea pig brain membranes and [^{3}H](+)-pentazocine (σ_1 receptors) or with rat liver membranes and [^{3}H]DTG in the presence of 1 μM dextrallorphan (σ_2 receptors) as described in Methods. IC_{50} values were determined using iterative curve-fitting program GraphPAD InPlot (San Diego, CA). IC_{50} values were then converted to apparent K_i values using the Cheng−Prusoff equation and radioligand K_d values. Values are the averages of two or three experiments, ±SEM. Each experiment was carried out in duplicate.

arylethylenediamines, we had noticed that (aminoethyl)piperidine and (aminoethyl)homopiperidine possessing iodobenzamides/arylethylenediamines had the highest potency for σ_1 and σ_2 receptor subtypes. On the basis of these results, we hypothesized that the aromatic group occupies the lipophilic pocket of the receptors and the alkylamino group represent the pharmacophore; therefore substituted sulfonamides possessing aminoethyl piperidines and aminoethylhomopiperidines should have high binding affinities for σ receptors. The results of our binding experiments showed that aromatic sulfonamides such as 4-iodo-*N*-[2-(1′-piperidinyl)ethyl]benzenesulfonamide, **6**, and *N*-[2-(1′-homopiperidinyl)ethyl]-4-iodobenzenesulfonamide, **8**, had high affinities for σ_1 sites (K_i = 0.75 and 2.14 nM, respectively). Potency for σ_2 sites for both **6** and **8** were modest (K_i = 206 and 189 nM, respectively). The binding affinity for the corresponding diethyl and pyrrolidine derivatives **2** and **4**, however, were lower for σ_1 as well as σ_2 sites (Table 2). This is consistent with our previous findings with iodobenzamides. Tertiary sulfonamides **9** and **10** both had subnanomolar affinity for σ_1 receptor subtypes (K_i = 0.18 and 0.14 nM, respectively) and also an 8−9-fold increase in σ_2 affinities (44.4 and 23.5 nM, respectively) over the corresponding secondary sulfonamide **7** and **8**. The incorporation of a 4-methoxy substituent in the 3-iodinated arylsulfonamides **11** and **12** reduced the receptor binding affinity for σ_1 and σ_2 sites as well. The reduced affinity for σ sites was also observed for the methoxy-substituted benzamides.[25] A patent literature search indicated that several substituted arylhalosulfonamides have been reported as antiarrhythmics.[27,28]

The preparation of 4-[^{125}I]iodo-*N*-[2-(1′-piperidinyl)-ethyl]benzenesulfonamide, **6b**, was achieved in high yields starting from the stannylated derivative **6a**. The radioiodinated benzenesulfonamide was purified using reversed phase HPLC. The retention time of the labeled compound using MeOH/phosphate buffer (10 mM): 80/20 was about 9 min. The σ receptor pharmacology was established by in vitro competition binding studies using

Table 3. Inhibition Constants (IC_{50}, nM; ±SEM) for 4-[^{125}I]IPBS Binding in Guinea Pig Brain Membranes[a]

compd	IC_{50}
BD1008	0.70 ± 0.18
4-IPBS	1.46 ± 0.13
haloperidol	6.28 ± 0.11
(+)-pentazocine	10.4 ± 1.1
DTG	87.2 ± 15
(−)-pentazocine	152 ± 0.2

[a] Confirmation of σ-like pharmacological profile of 4-[^{125}I]IPBS binding was carried out in guinea pig brain membranes. Guinea pig brain membranes (300−500 μg of membrane protein) were incubated with 0.3 nM 4-[^{125}I]IPBS and 12 concentrations of unlabeled test ligand ranging from 0.05 to 10 000 nM. Incubations were carried out in 50 mM Tris-HCl, pH 8.0, at 25 °C for 60 min in a final volume of 0.25 mL. Nonspecific binding was determined in the presence of 10 μM haloperidol. All other procedures and data analysis were described in caption to Table 1 for assays using tritiated ligand, with the exception that counting was carried out in a gamma counter (LKB model 1272 CLINIGAMMA). Values are the averages of two experiments, ±SEM. Each experiment was carried out in duplicate. The data are presented as IC_{50} values and not K_i since the K_d value for 4-[^{125}I]IPBS in guinea pig brain membranes was not directly determined. However, due to the low concentration of radioligand used, the K_i values will closely approximate the IC_{50} values.

σ ligands and guinea pig brain membranes. The rank order of potency was BD1008 (*N*-[2-(3,4-dichlorophenyl)-ethyl]-*N*-methyl-2-(1-pyrrolidinyl)ethylamine) > IPBS > haloperidol > (+)-pentazocine > DTG (1,3-di-*o*-tolylguanidine) > (−)-pentazocine. The inhibition constants (IC_{50}) were 0.70, 1.46, 6.28, 10.4, 87.2, and 152 nM, respectively (Table 3). These IC_{50} values and the rank order of potency are consistent with the labeling of σ_1 receptors.

To evaluate the tumor imaging potential of HAS, the biodistribution of 4-[^{125}I]IPBS was studied in C57 black mice bearing B16 murine melanoma tumors. A recent study found that the melanoma uptake in the C57 black mice animal model compared well with melanoma patients.[22] For this reason, the C57/B16 melanoma model was chosen for this study. A high tumor uptake of the radiopharmaceutical was found (7.40% ID/g) at

Table 4. Tissue Distribution of 4-[^{125}I]Iodo-*N*-[2-(1′-piperidinyl)ethyl]benzenesulfonamide, 4-[^{125}I]IPBS, in C57 Black Mice Bearing B16 Melanoma Tumor Xenograft (%ID/g ± SD; $n = 4$)

organ	1 h	6 h	24 h
blood	3.67 ± 1.27	2.26 ± 1.49	0.31 ± 0.21
heart	5.21 ± 2.69	2.02 ± 0.32	0.09 ± 0.03
liver	3.54 ± 1.56	3.15 ± 0.60	0.15 ± 0.06
lung	10.90 ± 4.97	5.24 ± 0.98	0.18 ± 0.12
kidneys	6.48 ± 3.23	3.43 ± 0.52	0.77 ± 0.49
spleen	10.84 ± 5.19	10.45 ± 1.35	0.13 ± 0.04
stomach	5.89 ± 2.43	3.83 ± 1.08	0.23 ± 0.18
sm intest	7.67 ± 3.15	6.23 ± 0.70	0.35 ± 0.29
lg intest	3.00 ± 1.25	7.91 ± 1.31	0.30 ± 0.11
brain	3.85 ± 2.15	7.7 ± 2.68	0.06 ± 0.01
tumor	7.40 ± 0.52	7.22 ± 1.70	1.54 ± 0.22
ratio tumor/blood	2.02 ± 0.41	3.19 ± 1.14	4.97 ± 1.05

1 h postinjection (Table 4). The tumor activity was found to be constant (7.22% ID/g) at 6 h postinjection, indicating slow wash out of the activity from the tumor. Although there was a relatively slow clearance from blood and other normal organs at 1 and 6 h postinjection, tumor had the highest (1.54% ID/g) activity at 24 h postinjection. Tumor to blood and tumor to liver ratios were about 5 and 10, respectively, at 24 h postinjection. These results show that 4-[^{125}I]iodo-*N*-[2-(1′-piperidinyl)ethyl]benzenesulfonamide clearly has potential for imaging melanoma tumors.

In conclusion, the discovery of a new σ receptor binding ligand class, HAS, is reported. Several haloarylsulfonamides possessed high affinity for σ binding sites, particularly σ_1 sites where subnanomolar affinity was observed. A radioiodinated benzenesulfonamide, 4-[^{125}I]IPBS, was synthesized in high yields. A pilot biodistribution study in C57 black mice possessing a melanoma xenograft showed high tumor uptake and slow wash out of the activity from tumor, showing the neoplastic disease imaging potential of radioiodinated benzenesulfonamides. Further SAR/biodistribution studies are in progress in order to develop an optimal compound that may be clinically useful.

Experimental Section

General Experimental Methods. Reagents for organic syntheses were purchased from Aldrich Chemical Co., Milwaukee, WI, and used without further purification. HPLC grade solvents were purchased from Fisher Scientific Co. and used without further distillation. Proton NMR spectra were recorded on a Bruker 300 AM spectrometer. NMR peak patterns were described by the following abbreviations: s = singlet, b = broad, d = doublet, t = triplet, q = quartet, m = multiplet, and arom = aromatic protons. Chemical shifts were expressed as ppm using $CDCl_3$ as internal standard. Low-resolution chemical ionization mass spectra were performed on a Finnigan 1015 mass spectrometer. Thin-layer chromatography (TLC) was performed on Analtech uniplate silica gel GF plates (250 μm, 10 × 20 cm) and developed with $CHCl_3$/MeOH: 90/10. Elemental analysis were performed by Quantitative Technologies Inc. (Whitehouse, NJ). Radio-thin-layer chromatography (radio-TLC) was performed using a radiochromatogram scanner (Packard 7220/21). Sodium iodide-I-125, Na^{125}I, was obtained from Amersham (Arlington Heights, IL). Radioactivity was measured using a Capintec radioisotope calibrator CRC-4. 1,3-[^{3}H]Di-*o*-tolylguanidine, ([^{3}H]DTG, 35.4 Ci/mmol) was bought from DuPont/NEN (Boston, MA). [^{3}H]-(+)-Pentazocine (51.7 Ci/mmol) was synthesized as described previously.[26a,b] Dextrallorphan was provided by Dr. F. I. Carroll (Research Triangle Institute, Research Triangle Park, NC). Haloperidol, Tris-HCl, and polyethyleneimine were purchased from Sigma Chemical Co. (St. Louis, MO).

***N*-(2-(Diethylamino)ethyl)-4-bromobenzenesulfonamide, 1.** *N*,*N*-Diethylethylenediamine (0.422 g, 3.63 mmol) was suspended in $CHCl_3$ (50 mL) and 50% aqueous $NaHCO_3$ (50 mL), and 4-bromobenzenesulfonyl chloride (1.0 g, 3.92 mmol) in $CHCl_3$ (10 mL) was added to the mixture. The solution was stirred at room temperature for 15 h. The organic layer was separated, washed with water, and evaporated to dryness. The resulting oil was chromatographed on a silica gel column and eluted with EtOAc/NEt_3: 100/2 (v/v). The desired fractions were pooled and the volatiles removed in vacuo to give a colorless oil (1.1 g, 95%). ^{1}H NMR ($CDCl_3$) 0.85−0.90 (t, 6H, NCH_2CH_3); 2−30−2.35 (q, 4H, NCH_2CH_3); 2.47−2.51 (m, 2H, NCH_2); 2.95−2.99 (m, 2H, NCH_2); 7.62−7.64 (d, 2H, arom); 7.70−7.74 (d, 2H, arom).

***N*-(2-(Diethylamino)ethyl)-4-iodobenzenesulfonamide, 2.** This compound was prepared by the same procedure as above from 4-iodobenzenesulfonyl chloride (1.0 g, 3.3 mmol) and *N*,*N*-diethylethylenediamine (0.42 g, 3.7 mmol) in 88% yield as a colorless oil (1.2 g). ^{1}H NMR ($CDCl_3$): 0.85−0.90 (t, 6H, CH_3); 2.30−2.37 (q, 4H, NCH_2); 2.41−2.44 (t, 2H, NCH_2); 2.79−2.83 (t, 2H, NCH_2); 7.54−7.57 (d, 2H, arom); 7.83−7.86 (d, 2H, arom).

***N*-[2-(1′-Pyrrolidinyl)ethyl]-4-bromobenzenesulfonamide, 3.** This compound was prepared by the same procedure as above from 4-bromobenzenesulfonyl chloride (1.0 g, 3.92 mmol) and 1-(2-aminoethyl)pyrrolidine (0.45 g, 3.94 mmol) in 88% yield as a white solid (1.1 g), mp 76−78 °C. ^{1}H NMR ($CDCl_3$): 1.66−1.73 (m, 4H CH_2CH_2); 2.29−2.34 (m, 4H, CH_2-NCH_2); 2.48−2.51 (m, 2H, NCH_2); 2.95−2.99 (m, 2H, NCH_2); 7.62−7.65 (d, 2H, arom); 7.70−7.73 (d, 2H, arom).

***N*-[2-(1′-Pyrrolidinyl)ethyl]-4-iodobenzenesulfonamide, 4.** This was prepared using same procedure as **1** from 4-iodobenzenesulfonyl chloride (1.0 g, 3.3 mmol) and 1-(2-aminoethyl)pyrrolidine (0.42 g 3.7 mmol) in 89% yield as beige solid (1.1 g), mp 71−73 °C. ^{1}H NMR ($CDCl_3$): 1.65−1.70 (m, 4H, CH_2); 2.30−2.34 (m, 4H, NCH_2); 2.49−2.54 (m, 2H, NCH_2); 2.94−3.0 (m, 2H, NCH_2); 7.52−7.58 (d, 2H, arom); 7.84−7.87 (d, 2H, arom). This compound has been previously reported in the patent literature.[27,28]

***N*-[2-(1′-Piperidinylethyl)]-4-bromobenzenesulfonamide, 5.** This compound was prepared from 4-bromobenzenesulfonyl chloride (1.0 g, 3.92 mmol) and 1-(2-aminoethyl)-piperidine (0.50 g, 3.9 mmol) in 92% yield (1.2 g), mp 91−92 °C. ^{1}H NMR ($CDCl_3$): 1.39−1.43 (m, 6H, pip CH_2s); 2.16−2.34 (bm, 4H, piperidinyl CH_2NCH_2); 2.30−2.34 (t, 2H, NCH_2); 2.91−2.95 (t, 2H, NCH_2); 7.62−7.64 (d, 2H, arom); 7.69−7.73 (d, 2H, arom).

***N*-[2-(1′-Piperidinyl)ethyl]-4-iodobenzenesulfonamide, 6.** This compound was prepared from 4-iodobenzenesulfonyl chloride (1.0 g, 3.3 mmol) and 1-(2-aminoethyl)-piperidine (0.43 g, 3.4 mmol) in 92% yield (1.2 g), mp 100−102 °C. ^{1}H NMR ($CDCl_3$): 1.40−1.49 (m, 6H, CH_2); 2.18−2.21 (bm, 4H, NCH_2); 2.34−2.37 (m, 2H, NCH_2); 2.94−2.98 (m, 2H, NCH_2); 7.55−7.58 (d, 2H, arom); 7.84−7.86 (d, 2H, arom).

***N*-[2-(1′-Piperidinyl)ethyl]-4-tri-*n*-butylstannylbenzenesulfonamide, 6a.** *N*-[2-(1′-Piperidinylethyl)]-4-iodobenzenesulfonamide (500 mg, 1.3 mmol) in NEt_3/THF (25/15 mL), tetrakis(triphenylphosphine)palladium(0) (0.29 g, 0.2 equiv), and bis(tri-*n*-butyltin) (1.1 g, 1.9 mmol, 1.5 equiv) were heated at reflux for 4 h. Additional bis(tributyltin) (0.55 g) was added to the reaction mixture and heated at reflux overnight. The solvents were removed in vacuo, and the residue was dissolved in a small quantity of hexanes/EtOAc (50/50, v/v) and loaded on a silica gel column packed with hexanes and eluted with hexanes/EtOAc. The fractions containing the desired compound were pooled together, and the volatiles were removed to give a light yellow oil (0.18 g, 25%). ^{1}H NMR ($CDCl_3$): 0.83−0.90 (m, 9H, CH_3); 1.03−1.09 (t, 6H, CH_2 from ^{n}Bu); 1.25−1.50 (m, 18H, CH_2s from ^{n}Bu and piperidinyl ring); 2.0−2.2 (bm, 5H, NCH_2); 2.3−2.4 (m, 2H, NCH_2); 2.8−2.9 (m, 2H, CH_2); 7.56−7.59 (d, 2H, arom); 7.74−7.77 (d, 2H, arom).

***N*-[2-(1′-Homopiperidinyl)ethyl]-4-bromobenzenesulfonamide, 7.** **7** was prepared from 4-bromobenzenesulfonyl chloride (1.3 g, 5.1 mmol) and 1-(2-aminoethyl)homopiperidine (0.73 g, 5.1 mmol) in 95% yield (1.7 g), mp 82−84 °C. ^{1}H NMR ($CDCl_3$): 1.52 (bs, 8H, homopip CH_2); 2.40−2.42 (m, 4H, homopip NCH_2); 2.48−2.51 (m, 2H, NCH_2); 2.88−2.92 (m, 2H, NCH_2); 7.62−7.64 (d, 2H, arom); 7.71−7.74 (d, 2H, arom).

***N*-[2-(1′-Homopiperidinyl)ethyl]-4-iodobenzenesulfonamide, 8.** This was prepared from 4-iodobenzenesulfonyl chloride (1.0 g, 3.33 mmol) and 1-(2-aminoethyl)homopiperidine (0.52 g, 3.6 mmol) to give 86% (1.2 g) of desired compound as a colorless oil. ^{1}H NMR ($CDCl_3$): 1.52 (bs, 8H, homopip CH_2); 2.40−2.42 (m, 4H, homopip NCH_2); 2.48−2.51 (m, 2H, NCH_2); 2.88−2.92 (m, 2H, NCH_2); 7.62−7.64 (d, 2H, arom); 7.71−7.74 (d, 2H, arom).

***N*-[2-(1′-Homopiperidinyl)ethyl]-*N*-methyl-4-bromobenzenesulfonamide, 9.** This compound was prepared from 4-bromobenzenesulfonyl chloride (1.3 g, 5.1 mmol) and *N*-methyl-2-(1′-homopiperidinyl)ethylamine (0.80 g, 5.1 mmol) in 91% (1.7 g) yield. ^{1}H NMR ($CDCl_3$): 1.55 (bs, 8H, homopip CH_2); 2.59−2.68 (m, 6H, NCH_2); 2.79 (s, 3H, NCH_3); 3.07−3.11 (s, 2H, NCH_2); 7.64 (bs, 4H, arom).

***N*-[2-(1′-Homopiperidinyl)ethyl]-*N*-methyl-4-iodobenzenesulfonamide, 10.** This compound was prepared from 4-iodobenzenesulfonyl chloride (1.0 g, 3.3 mmol) and *N*-methyl-2-(1′-homopiperidinyl)ethylamine (0.52 g, 3.3 mmol) in 92% yield (1.3 g). ^{1}H NMR ($CDCl_3$): 1.55 (bs, 8H, homopip CH_2); 2.59−2.68 (6H, NCH_2); 2.78 (s, 3H, NCH_3); 3.06−3.11 (t, 2H, NCH_2); 7.47−7.50 (d, 2H, arom); 7.83−7.86 (d, 2H, arom).

***N*-[2-(1′-Piperidinyl)ethyl]-4-methoxybenzenesulfonamide, 11a.** To an ice-cold solution of 1-(2-aminoethyl)-piperidine (1.28 g, 1.0 mmol) in chloroform (50 mL) and NEt_3 (5 mL) was added 4-iodobenzenesulfonyl chloride (2.06 g, 1.0 mmol). The mixture was stirred overnight. The solvent was evaporated in vacuo, and the residue obtained was suspended in $CHCl_3$ (40 mL) and washed with saturated solution of $NaHCO_3$. The organic layer was separated, dried, and evaporated to dryness to give a light yellow oil (2.8 g, 94%). ^{1}H NMR ($CDCl_3$): 1.36−1.50 (m, 6H, piperidine CH_2s); 2.22−2.26 (bm, 4H, piperidine CH_2s); 2.27−2.31 (m, 2H, NCH_2); 2.88−2.92 (m, 2H, CH_2); 3.85 (s, 3H, OMe); 6.94−6.97 (d, 2H, arom); 7.76−7.79 (d, 2H, arom).

***N*-[2-(1′-Piperidinyl)ethyl]-3-iodo-4-methoxybenzenesulfonamide, 11.** A round-bottom flask was charged with **11a** (1.1 g, 3.7 mmol) in CCl_4 (10 mL). A solution of $Tl(CF_3CO_2)_3$ in CF_3CO_2H (15 mL) was added to the mixture. Iodine (0.48 g, 1.9 mmol) was added, and the reaction contents were heated at reflux for 2 h. The volatiles were removed in vacuo, the residue was basified with 10% aqueous NaOH, $CHCl_3$ (30 mL) was added to the residue, and the mixture was stirred for 15 min. The contents were filtered through a pad of Celite, and the organic layer was separated, washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness to give a white solid (1.3 g, 83%). ^{1}H NMR ($CDCl_3$): 1.37−1.49 (m, 6 H, piperidinyl CH_2s); 2.17 (bm, 4H, piperidinyl CH_2); 2.29−2.33 (m, 2H, NCH_2); 2.89−2.93 (m, 2H, NCH_2); 3.93 (s, 3H, OMe); 6.83−6.86 (d, 1H, arom); 7.80−7.83 (dd, 1H, arom); 8.22−8.23 (d, 1H, arom).

***N*-[2-(1′-Homopiperidinyl)ethyl]-*N*-methyl-4-methoxybenzenesulfonamide, 12a.** This compound was prepared by the same method as **1** using 4-methoxybenzenesulfonyl chloride (2.0 g, 9.7 mmol) and *N*-methyl-2-(1′-homopiperidinyl)-ethylamine (1.44 g, 9.5 mmol) to give **12a** as a colorless oil in 93% yield (2.9 g). ^{1}H NMR ($CDCl_3$): 1.54 (bs, 8H, homopip CH_2); 2.58−2.65 (m, 6H, NCH_2); 2.74 (s, 3H, N−CH_3); 3.15−3.19 (m, 3H, NCH_2); 3.83 (s, 3H, OMe); 6.93−6.96 (d, 2H, arom); 7.68−7.71 (d 2H, arom).

***N*-[2-(1′-Homopiperidinyl)ethyl]-*N*-methyl-3-iodo-4-methoxybenzenesulfonamide, 12.** A round-bottom flask was charged with **12a** (1.0 g, 3.1 mmol) in CF_3CO_2H (15 mL) and CCl_4 (10 mL) and $Tl(CF_3CO_2)_3$ (1.3 g, 2.3 mmol, 0.75 equiv). The mixture was stirred at room temperature until all thallium salt dissolved, and then iodine (0.4 g, 1.6 mmol, 0.52 eq) was added. The above mixture was heated at reflux for 1.5 h, and the volatiles were then removed in vacuo. The residue was taken up in ice cold water (20 mL), and 10% NaOH solution (10 mL) and $CHCl_3$ (40 mL) was added. The mixture was stirred at room temperature for 30 min to give a brown precipitate. This solid was filtered, and the organic layer was separated, dried, and evaporated in vacuo to give a light yellow oil (1.2 g, 85%). ^{1}H NMR ($CDCl_3$): 1.56 (bm, 8H, homopiperidine CH_2s); 2.63−2.71 (m, 6H, NCH_2); 2.77 (s, 3 H, NCH_3); 3.07−3.13 (m, 2H, NCH_2); 3.93 (s, 3H, OCH_3); 6.84−6.87 (dd, 1H, arom); 7.77−7.80 (dd, 1H, arom); 8.15 (s, 1H, arom).

Synthesis of [^{125}I]*N*-[2-(1′-piperidinyl)ethyl]-4-iodobenzenesulfonamide, 6b. An ethanolic solution of *N*-[2-(1′-piperidinyl)ethyl]-4-(tri-*n*-butylstannyl)benzenesulfonamide, **6a** (1.0 mg/mL), was prepared. To 100 μL of this solution was added $Na^{125}I$ (1.0−2.0 mCi, 10−15 μL, in 0.1 N NaOH), followed by the addition of 0.05 N HCl (50−100 μL) to adjust the pH to between 4.0 and 5.5. A freshly prepared solution (100 μL) of chloramine-T (1 mg/mL) was added to the above mixture, and the solutions were incubated at room temperature for 15 min. After this time 200 μL of sodium metabisulfite (10 mg/mL) was added and incubated for 5 min. Finally, a saturated solution of sodium bicarbonate (500 μL) was added to the reaction vial, and the radioactivity was extracted (89−93%) with chloroform (2 × 1 mL). The organic layer was separated and evaporated in a stream of air. The residue was dissolved in MeOH (400 μL) and injected into HPLC fitted with a reversed phase C_{18} column (Z module) and eluted with MeOH/phosphate buffer (80/20; 10 mM, pH = 7.2). The retention time at a flow rate of 1.0 mL/min was about 9 min. The fractions containing the desired compound were pooled and cospotted on TLC along with authentic "cold" 4-iodo-*N*-[2-(1′-piperidinyl)ethyl]benzenesulfonamide, and developed in $CHCl_3$/MeOH: 90/10. The combined fractions were reduced in volume by evaporation under a stream of nitrogen, and the residue was suspended in normal saline or phosphate buffer (pH =7.2) and used for further binding/animal studies. The yield of HPLC purified **6b** was 77%, the radiochemical purity was >99%.

Pharmacology. σ_1 Receptor Binding Assays. The in vitro σ_1 binding affinity of nonradioactive sulfonamides were determined using the σ_1 selective probe [^{3}H](+)-pentazocine and guinea pig brain membranes.[26a] Guinea pig brain membranes (300−500 μg of membrane protein) were incubated with 3 nM [^{3}H](+)-pentazocine in a total volume of 0.5 mL of 50 mM Tris-HCl, pH 8.0. Incubations were carried out for 120 min at 25 °C. Nonspecific binding was determined in the presence of 10 μM haloperidol. Assays were terminated by dilution with 5 mL of ice cold 10 mM Tris-HCl, pH 8.0, and vacuum filtered through glass fiber filters using a Brandel cell harvester (Gaithersburg, MD). Filters were then washed twice with 5 mL of ice cold 10 mM Tris-HCl, pH 8.0. Filters were soaked in 0.5% polyethyleneimine for at least 30 min at 25 °C prior to use. Filters were counted in CytoScint cocktail (ICN, Costa Mesa, CA) after an overnight extraction of counts. Membranes were prepared from frozen guinea pig brains (minus cerebella) as previously described.[26a]

σ_2 Receptor Binding Assays. σ_2 receptors were labeled as previously described using rat liver membranes, a rich source of σ_2 sites, and [^{3}H]-1,3-di-*o*-tolylguanidine ([^{3}H]DTG) in the presence of 1 μM dextrallorphan to mask σ_1 receptors.[29] Assays were performed in 50 mM Tris-HCl, pH 8.0, for 120 min at 25 °C in a volume of 0.5 mL with 150−200 μg of membrane protein and 5 nM radioligand. Nonspecific binding was determined in the presence of 10 μM haloperidol. All other manipulations were as described above for σ_1 receptor assay. Rat liver membranes were prepared from the livers of male Sprague−Dawley rats as described.[29]

Cell Culture. B16 melanoma tumor cells were purchased from ATCC, Rockville, MD, and cultured in serum-supplemented RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (GIBCO) at 37 °C. The cells were adherent and split weekly in a 1:5 ratio using trypsin/EDTA (GIBCO).

The cells were grown in T75 cell culture flasks. When confluent the cells were detached using trypsin/EDTA (0.025%) or scraped with a cell scraper in DMEM.

In Vivo Distribution. C57 black mice (Charles-River, Wilmington, MA) weighing 25−32 g were injected with about 1.0 million B16 murine melanoma cells in the right flank. After about 10 days the tumors were visible, and the animals were injected in the tail vein with radiolabeled 4-[^{125}I]iodo-*N*-[2-(1′-piperidinyl)ethyl]benzenesulfonamide, **6b**, to study the in vivo tumor imaging potential. The animals were sacrificed at 1, 6, and 24 h post iv injection under ketamine/xylazine anesthesia as previously described.[19] The organs were excised, dried on absorbent paper, and placed in preweighed test tubes, and the radioactivity was assayed in an automatic gamma counter (Packard, CobraII Autogamma, Meriden, CT). The %ID/g of organ values were determined by comparison of the tissue radioactivity with suitably diluted aliquots of the injected dose and divided by the weight of the organ.

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