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Communications to the Editor

1′-Benzyl-3,4-dihydrospiro[2*H*-1-benzothiopyran-2,4′-piperidine] (Spipethiane), a Potent and Highly Selective σ_1 Ligand

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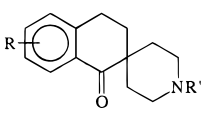
Much effort has been devoted to the solution of the so-called "sigma (σ) enigma".[1] Since the introduction of the term "σ receptor" in 1976,[2] many ligands displaying high affinity for these sites have been discovered.[3−5] However, after more than two decades of research, little is known about the biochemical and molecular nature of these sites. The σ receptor concept itself has been questioned for the lack of a specific endogenous agonist and for its undefined biological role.[5,6] Thus, σ sites should not be classified as receptors in the sense of being agonist-activated mediators of signal transduction, and the debate continues over whether σ sites are true receptors or a membrane bound enzyme.[6] The situation has been complicated further by the observation that σ sites do not constitute a homogeneous population and they can be divided into at least two different subtypes, namely σ_1 and σ_2.[5,7] However, additional σ sites have been proposed on the basis of their distinct pharmacological profiles versus the previously defined σ_1 and σ_2 subtypes. Thus a putative σ_3 and another site were shown to display high affinity for certain phenylamino-tetralines[8,9] and arylethylenediamine-related compounds,[10,11] respectively.

Very recently, the existence of σ sites has been confirmed by the cloning of a guinea pig σ_1 receptor[12] and a human σ_1 receptor.[13] The amino acid sequence of these cloned receptors, having a single putative transmembrane domain, bears significant homology (93% identity and 96% similarity) to each other. Interestingly, the amino acid sequence of this receptor shows no homology to known mammalian proteins but shares 30% identity with a gene product of yeast, a gene that encodes a sterol C8−C7 isomerase of the ergosterol biosynthetic pathway. On this basis, it has been advanced that a possible common denominator of σ receptor function might be sterol biosynthesis.[6] However, other evidence indicates that σ receptors might be coupled to G-proteins as well.[14]

The growing interest about σ receptor ligands can be related to the fact that these receptors may represent new targets for the development of therapeutic agents for the treatment of various mental, motor, and other disorders.[1] However, a major problem in σ receptor research is the lack of specific σ ligands as most of these agents bind at other receptor systems including serotonin 5-HT_2, dopamine D_2, PCP (1-(1-phenylcyclohexyl)-piperidine), and muscarinic receptors, thus making still unclear as to whether their pharmacological properties are due to the interaction with σ sites. Consequently, it is of paramount importance to make available selective ligands not only for the characterization of the σ sites but also for the development of new therapeutically useful agents. A vast array of structurally unrelated compounds interact with σ sites, suggesting that these receptors may be primordial, which makes it inherently difficult to determine the structural requirements leading to receptor subtypes selectivity.[3−5] Among the variety of these structures, spirotetralines **1** were reported to be potent σ ligands.[15] However, these



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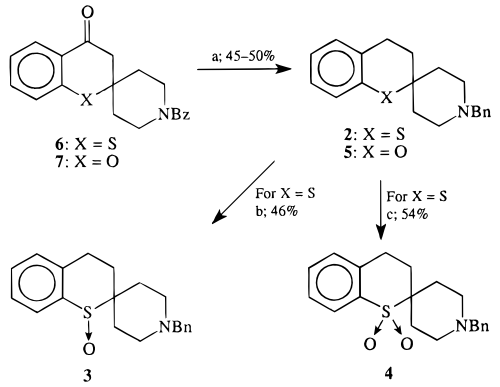
Scheme 1. Synthesis of Spiropiperidines **2**−**5**[a]



[a] Bz = benzoyl, Bn = benzyl; reaction conditions: (a) BH_3·Me-SMe, diglyme, 120 °C, 14 h; then MeOH, room temperature, 5 h, HCl, 120 °C, 3 h; (b) 30% H_2O_2, CH_3COOH, room temperature, 18 h; (c) 30% H_2O_2, CH_3COOH, room temperature, 42 h.

ligands displayed also significant affinity for serotonin 5-HT_2 receptors which may add therapeutic value for treating psychotic disorders but in the meantime may complicate the characterization of σ sites. We thought it worthwhile to modify the structure of **1** to improve affinity for σ_1 receptors such as to discriminate hopefully among σ sites and other receptor systems. We report here the synthesis and preliminary characterization in binding and functional experiments of 1′-benzyl-3,4-dihydrospiro[2*H*-1-benzothiopyran-2,4′-piperidine] (**2**, spipethiane) and of its corresponding sulfoxide (**3**) and sulfone (**4**). To verify the role of the sulfur atom of **2** in the interaction with σ sites, 1′-benzyl-3,4-dihydrospiro-[2*H*-1-benzopyran-2,4′-piperidine] (**5**) has been included in this study. Compound **5** has been disclosed to be an inhibitor of histamine release,[16] but no data on its σ binding affinity has been published.

Chemistry. The compounds were synthesized by standard procedures (Scheme 1) and were characterized by ^{1}H NMR and elemental analysis.[17] Reduction of **6**[18] and **7**[18] with borane afforded **2**[19] and **5**,[20] respectively. Treatment of sulfide **2** with different amounts of H_2O_2 gave the corresponding sulfoxide **3**[21] and sulfone **4**.[22]

Pharmacology. Compounds **1**−**5**, in the form of hydrogen oxalate salts, were evaluated for in vitro activity on σ_1, σ_2, serotonin 5-HT_2, dopamine D_2, muscarinic M_2, muscarinic M_3, opioid, and PCP receptors and α_{1A}- and α_{1B}-adrenoreceptors. The detailed methods have been published previously.[23−30] The following specific ligands, tissue sources, and procedures were used: (a) σ_1 receptors, [^{3}H]-(+)-pentazocine, guinea pig brain;[23] (b) σ_2 receptors, [^{3}H]DTG in the presence of 200 nM (+)-*N*-allylnormetazocine (NANM), guinea pig brain;[24] (c) serotonin 5-HT_2 receptors, [^{3}H]ketanserin, guinea pig frontal cortex;[25] (d) dopamine D_2 receptors, [^{3}H]spiperone, rat striatum;[26] (e) muscarinic M_2 receptors, [^{3}H]NMS, rat heart;[27] (f) muscarinic M_3 receptors, [^{3}H]NMS, rat submaxillary gland;[27] (g) total opioid receptors, [^{3}H]naloxone, rat whole brain;[28] (h) α_{1A}-adrenoreceptors, [^{3}H]prazosin, rat submaxillary gland;[29] (i) α_{1B}-adrenoreceptors, [^{3}H]prazosin, rat liver;[29] (j) PCP receptors, [^{3}H](+)NANM in the presence of 5 μM haloperidol, rat brain.[30] Nonspecific binding for each receptor was defined by inclusion of 1 μM haloperidol (σ_1, σ_2, and D_2), 1 μM methylsergide (5-HT_2), 1 μM atropine (M_2 and M_3), 1 μM naloxone (total opioid), 10 μM phentolamine (α_{1A} and α_{1B}), and 10 μM (+)-NANM (PCP). The following reference compounds were used: (+)-pentazocine (σ_1 receptors), haloperidol (σ_2 and D_2 receptors), clozapine (5-HT_2 receptors), methoctramine (muscarinic M_2 and M_3 receptors), morphine (opioid receptors), prazosin (α_{1A}- and α_{1B}-adrenoreceptors), and methaphit (PCP receptors). Moreover, the affinity of compounds **1** and **2** for the σ-like site known as σ_3[31,32] was evaluated on guinea pig brain homogenates prepared as reported,[32] in competition for sites labeled by [^{3}H]ketanserin (1 nM) in the presence of 10 μM serotonin to mask 5-HT receptors. Previously, Booth et al.[33] have reported that ketanserin displays high affinity for σ_3 binding sites (K_i = 0.38 nM) while serotonin does not recognize this site (K_i < 5000 nM). Therefore, lacking a σ_3 radiolabeled ligand, we decided to adopt this strategy to label σ_3 sites occurring in guinea pig brain homogenates. Binding estimates were expressed as IC_{50} or K_i values derived using the Cheng−Prusoff equation[34] and calculated using the LIGAND or EBDA programs.[35]

Since σ_3 ligands are supposed to stimulate tyrosine hydroxylase (TH) activity in minces of rat corpus striatum at 0.1 μM, we investigated **1** and **2** following the procedure described for certain phenylaminotetralines.[31,32]

Results and Discussion. The results, expressed as K_i values, of spiropiperidines **2**−**5** are shown in Table 1 together with those of **1** and standard compounds. It can be seen that replacing the carbonyl group of **1** by sulfur or oxygen, affording **2** or **5**, respectively, or converting **2** into the corresponding analogues **3** and **4** alters markedly both affinity and selectivity toward σ_1 receptors. This finding clearly indicates that the insertion of a heteroatom such as sulfur or oxygen into the tetrahydronaphthalene ring of **1** is highly effective toward σ_1 receptors. However, the most striking result of the present investigation is the superpotent affinity and selectivity toward σ_1 receptors displayed by spipethiane (**2**). Interestingly, spipethiane as well as analogues **3**−**5** turned out to be devoid of significant affinity for the other receptor systems so far investigated. Particularly, spipethiane (**2**) showed a low affinity for the σ_3 binding site (IC_{50} = 632 ± 18 nM; n = 3), whereas the reference compound **1** displayed a 15-fold higher affinity for this binding site (IC_{50} = 42 ± 6 nM; n = 3). Furthermore, **1** and **2** were not able to increase TH activity (p > 0.05) up to 0.1 μM concentration. An analysis of affinity estimates in Table 1 reveals that the replacement of the carbonyl group of **1** by either sulfur as in **2** or oxygen as in **5** leads to an increase in affinity for σ_1 receptors, while producing a slight (2-fold for **5**) to marked (42-fold for **2**) decrease in affinity for σ_2 receptors. Thus, spipethiane (**2**) was 19-fold less potent than **5** at σ_2 receptors, and consequently it was markedly more selective than **5** toward σ_1 receptors. Oxidation of **2** into the corresponding sulfoxide **3** and sulfone **4** caused a significant (40−50-fold) decrease in affinity for σ_1 receptors whereas only a small (4-fold) decrease in affinity for σ_2 receptors. This finding parallels the results observed by Gilligan et al.[36] for compounds which are structurally related to spipethiane. However, these open analogues displayed also a significant affinity for D_2 and 5-HT_2 receptors that is not observed with the compounds used in the present

Table 1. Binding and Functional Data for Spipethiane (**2**) and Its Analogues **1** and **3**−**5**[a]

		K_i (nM)									
no.	X	σ_1	σ_2	σ_2/σ_1	5-HT_2	D_2	α_{1A}	α_{1B}	M_2	M_3	opioid	PCP
1	CO	1.4 ± 0.08	10 ± 3	7	218 ± 20	5500 ± 200	>10000	>10000	2700 ± 300	>10000	>10000	>10000
2	S	0.5 ± 0.02	416 ± 43	832	7600 ± 420	10400 ± 280	>10000	>10000	10800 ± 300	>10000	>10000	>10000
3	SO	25 ± 0.12	1700 ± 166	68	>10000	>10000	>10000	>10000	>10000	>10000	>10000	>10000
4	SO_2	20 ± 1.2	1800 ± 230	90	>10000	>10000	>10000	>10000	>10000	>10000	>10000	>10000
5	O	0.62 ± 0.07	22 ± 2.4	35	>10000	>10000	>10000	>10000	>10000	>10000	>10000	>10000
(+)-pentazocine		6.1 ± 0.9	1340 ± 84	220	nd	nd	nd	nd	nd	nd	nd	nd
haloperidol		3.2 ± 0.08	11.7 ± 1.8	4	16 ± 9	4.8 ± 1.5	nd	nd	nd	nd	nd	nd
clozapine		8500 ± 120	>10000		12 ± 4	nd	nd	nd	nd	nd	nd	nd
prazosin		nd	nd		nd	nd	1.05 ± 0.05	2.93 ± 0.80	nd	nd	nd	nd
methoctramine		nd	nd		nd	nd	nd	nd	15 ± 1.1	998 ± 130	nd	nd
morphine		nd	nd		nd	nd	nd	nd	nd	nd	32.5 ± 9	nd
methaphit		>10000	>10000		nd	nd	nd	nd	nd	nd	nd	16 ± 7

[a] K_i values ± SEM in nM are the mean of three determinations, each performed in duplicate, except for values >10000, which were obtained from two determinations. All Hill number (nH) were not significantly different from unity ($p > 0.05$). Equilibrium dissociation constants (K_i) were derived using the Cheng−Prusoff equation.[34] The radioligands and the tissues used for the binding studies were σ_1, [^{3}H]-(+)-pentazocine (guinea pig brain); σ_2, [^{3}H]DTG in the presence of 200 nM (+)-NANM (guinea pig brain); 5-HT_2, [^{3}H]ketanserin (guinea pig frontal cortex); D_2, [^{3}H]spiperone (rat striatum); α_{1A}, [^{3}H]prazosin (rat submaxillary gland); α_{1B}, [^{3}H]prazosin (rat liver); M_2, [^{3}H]NMS (rat heart); M_3, [^{3}H]NMS (rat submaxillary gland); opioid, [^{3}H]naloxone (rat whole brain); PCP, [^{3}H]-(+)-NANM in the presence of 5 μM haloperidol (rat brain). Abbreviation nd stands for not done.

investigation. The fact that the ligands currently used to investigate σ receptors lack not only a clear subtype selectivity but also σ receptor specificity may explain the difficulties in characterizing σ receptor subtypes with classic pharmacological studies. The results presented in this paper clearly show that the use of spipethiane (**2**) might help the pharmacological identification of σ receptor subtypes.

To our knowledge, spipethiane (**2**) represents, until now, one of the most potent and selective σ_1 receptor ligands, and it might be a valuable tool for the characterization of σ receptors.

Our future work in this area will include studies directed at gaining a better understanding of the intriguing trends noted above. In addition, we hope to develop relevant structure−activity relationships for σ receptor subtypes through the synthesis of chiral compounds related to those presented in this paper. These studies should contribute to clarify the structural requirements for selective binding of spiropiperidines to σ receptor subtypes.

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(17) ^{1}H NMR spectra were recorded on a Varian VXR 300 instrument. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), and spin multiplicities are given as s (singlet), dd (double doublet), t (triplet), or m (multiplet). The elemental analyses of the compounds agreed to within ±0.4% of the calculated value. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040−0.063 mm, Merck) by flash chromatography.

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(19) A solution of **6**[18] (1.4 g, 4.15 mmol) in dry diglyme (42 mL) was treated with a 10 M solution of BH_3·MeSMe (2.45 mL) in dry diglyme (3 mL). After 14 h at 120 °C under a stream of dry nitrogen, excess borane was destroyed by careful addition of MeOH (15 mL). The resulting mixture was left to stand for 5 h, treated with HCl gas, and then heated at 120 °C for 3 h. Removal of the solvent gave a residue that was purified by column chromatography, eluting with cyclohexane−ethyl acetate (9:1) to give **2** as the free base: 0.6 g (47% yield); mp 63−64 °C; ^{1}H NMR ($CDCl_3$) δ 1.72−1.95 (m, 4, 3′- and 5′-CH_2), 1.98 (t, 2, 3-CH_2), 2.41−2.82 (m, 4, 2′- and 6′-CH_2), 2.9 (t, 2, 4-CH_2), 3.58 (s, 2, CH_2Ph), 6.95−7.43 (m, 9, ArH). It was characterized as the oxalate salt: mp 213−214 °C (from 2-PrOH/EtOH). Anal. ($C_{20}H_{23}NS$·$C_2H_2O_4$·0.5H_2O) C, H, N, S.

(20) This compound was obtained from **7**[18] following the procedure described for **2**. The free base (oil) was purified by column chromatography, eluting with cyclohexane−ethyl acetate (8:2): 49% yield; ^{1}H NMR ($CDCl_3$) δ 1.58−1.94 (m, 6, 3-, 3′-, and 5′-CH_2), 2.39−2.73 (m, 4, 2′- and 6′-CH_2), 2.78 (t, 2, 4-CH_2), 3.57 (s, 2, CH_2Ph), 6.80−7.40 (m, 9, ArH). It was characterized as the oxalate salt: mp 208−210 °C (from EtOH). Anal. ($C_{20}H_{23}$-NO·$C_2H_2O_4$) C, H, N. This compound was synthesized by a different method:[16] mp (HCl salt) 240−241 °C.

(21) A solution of **2** (0.25 g, 0.808 mmol) and 30% H_2O_2 (0.36 mL) in AcOH (2.27 mL) was left at room temperature for 18 h, made basic with 2 N NaOH, and extracted with $CHCl_3$. Removal of the dried solvent (Na_2SO_4) gave an oil that was purified by column chromatography, eluting with ethyl acetate−MeOH (96:4) to give **3** as the free base: 0.12 g (46% yield); ^{1}H NMR ($CDCl_3$) δ 1.50−2.36 (br m, 6, 3-, 3′-, and 5′-CH_2), 2.37−2.90 (br m, 4, 2′- and 6′-CH_2), 2.97 (br m, 2, 4-CH_2), 3.59 (br s, 2, CH_2Ph), 7.18−7.50 (m, 8, ArH), 7.73 (dd, 1, 8-H). It was characterized as the oxalate salt: mp 214−215 °C (from EtOH). Anal. ($C_{20}H_{23}$-NOS·$C_2H_2O_4$) C, H, N, S.

(22) This compound was obtained from **2** following the procedure described for **3** using a 3-fold greater amount of 30% H_2O_2 and a reaction time of 42 h. The free base was purified by column chromatography eluting with cyclohexane−ethyl acetate (1:1): 54% yield; mp 143−145 °C; ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 2, 3′-CH_2), 2.35 (m, 4, 2′- and 5′-CH_2), 2.45 (t, 2, 3-CH_2), 2.89 (m, 2, 6′-CH_2), 2.98 (t, 2, 4-CH_2), 3.58 (s, 2, CH_2Ph), 7.13−7.60 (m, 8, ArH), 7.97 (dd, 1, 8-H). It was characterized as the oxalate salt: mp 220−222 °C (from EtOH). Anal. ($C_{20}H_{23}NO_2S$·$C_2H_2O_4$) C, H, N, S.

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