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Effects of linker elongation in a series of *N*-(2-benzofuranylmethyl)-*N*′-(methoxyphenylalkyl)piperazine σ_1 receptor ligands

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ABSTRACT

In our continued exploration of disubstituted piperazine derivatives as sigma (σ) receptor ligands with central nervous system (CNS) activity, a series of *N*-(2-benzofuranylmethyl)-*N*′-(methoxyphenylalkyl)piperazines (**16**–**21** and **26**–**31**) were synthesized, anticipating that these ligands would better suit the structural requirements of the current σ_1 pharmacophore. Affinities of these ligands for σ_1 and σ_2 receptors were investigated by means of radioligand binding assays, with the identification of *N*-(2-benzofuranylmethyl)-*N*′-[3-(4-methoxyphenyl)propyl]piperazine (**29**, K_i = 3.1 nM, σ_2/σ_1 = 45) as a selective σ_1 ligand. The σ_1 affinities and subtype selectivities of piperazines **16**–**21** and **26**–**31** were generally comparable to the corresponding benzylic analogs. Additionally, the affinities of **16**–**21** and **26**–**31** for the 5-HT_{2B} receptor were much lower than the relatively nonselective methoxybenzylic analogs **2**–**4**, indicating that elongation of the alkyl tether generally improved selectivity for σ_1 receptors.

Sigma (σ) receptors were first proposed as an opioid receptor subtype by Martin et al. in the mid-1970s.[1] Since that time, extensive pharmacological and behavioral studies have revealed that these sites are, in fact, biochemically and topographically distinct from all previously characterized mammalian proteins.[2–5] Two σ receptor subtypes, namely σ_1 and σ_2,[5,6] have been pharmacologically characterized and are widely distributed in both the central and peripheral nervous system (CNS and PNS, respectively).[7,8] Many historical, high affinity σ ligands, including haloperidol and 1,3-di-*o*-tolylguanidine (DTG), display little to no subtype selectivity.[9,10] However, σ receptor subtypes exhibit enantiodiscrimination toward certain structural classes, such as the benzomorphans. For example, [^{3}H](+)-pentazocine is the ligand of choice for in vitro σ_1 binding assays, displaying very high selectivity for the σ_1 subtype,[11] while (−)-pentazocine displays a preference for the σ_2 receptor.[5]

The σ_1 receptor has been cloned from numerous mammalian tissues, including human brain,[12] and the amino acid sequence is highly conserved, with greater than 90% homology across species.[13–15] Although σ_1 receptors primarily reside at the interface between the endoplasmic reticulum (ER) and mitochondria—the mitochondria-associated ER membrane (MAM)—and control Ca^{2+} flux by acting as molecular chaperones for type 3 inositol-1,4,5-triphosphate receptors, they are also able to translocate to the plasma membrane where they regulate Ca^{2+} and K^+ channels.[16–19]

The σ_2 receptor has yet to be cloned, but a molecular weight of approximately 21.5 kDa has been suggested based on the photoaffinity labeling of pheochromocytoma (PC12) cell membranes.[6,8] Compared to σ_1, much less is known about the function of σ_2 receptors, however, they are highly implicated in the regulation of cell proliferation and viability.[20]

The ability of σ receptors to regulate the neurotransmission mediated by acetylcholine,[21] dopamine,[22–24] glutamate[25] and 5-hydroxytryptamine,[26] accounts for their implication in a diverse spectrum of CNS disorders.[27,28] On the basis of their neuroregulatory and neuroprotective functions, agents acting at σ_1 have been proposed for the treatment of depression,[29,30] drug abuse[31,32] and psychiatric disorders.[33] Ligands selective for the σ_2 receptor, on the other hand, are proposed to act as novel antineoplastic agents.[34]

Work in our laboratory has focused on the rational design and development of increasingly σ subtype selective ligands, based on the differential arylalkyl disubstitution of 1,4-piperazine. We recently reported a series of *N*-(2-benzofuranylmethyl)-*N*′-benzylpiperazines (**1**–**4**, Fig. 1) as selective σ_1 receptor ligands.[35] The simple benzylic analog **1** was a highly selective σ_1 receptor ligand (K_i = 5.2 nM, σ_2/σ_1 = 46), with lower affinity for other CNS receptors, transporters, and ion channels. However, addition of a 2-, 3-, or 4-methoxy substituent (**2**, **3**, and **4**, respectively)—while retaining moderate to high affinity for the σ_1 receptor—also introduced concomitant high affinity for the 5-HT_{2B} receptor subtype, and micromolar affinity for the D_2 dopamine receptor.

The high degree of symmetry present in benzylpiperazines **1**–**4** provided little insight into the structural interactions important

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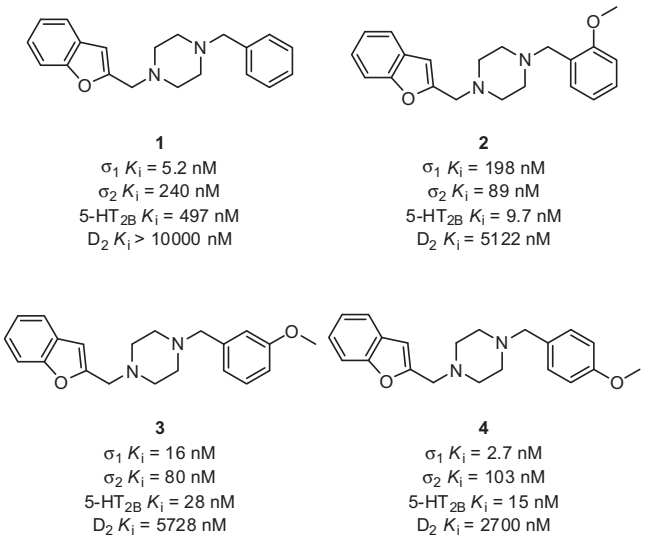


Figure 1. Examples of σ selective *N*-(2-benzofuranylmethyl)-*N*′-benzylpiperazines ligands.

for optimal σ_1 binding. However, Glennon et al. have generated a σ_1 receptor pharmacophore accounting for most of the structurally diverse family of σ_1 ligands (Fig. 2).[36] This pharmacophoric model requires a basic nitrogen flanked by two hydrophobic motifs; a primary hydrophobic region (typically an aryl group) at a distance of 6–10 Å from the central amine, and a sterically-tolerant secondary hydrophobic region 2.5–3.9 Å from the central nitrogen atom. The simplicity of the pharmacophore allows it to encompass most known σ_1 ligands, and guide the optimization of σ_1-binding chemotypes.[36,37]

The benzofuranyl group of **1** and its congeners are likely to occupy the secondary hydrophobic site of the Glennon pharmacophore, and extending the distance to the substituted phenyl ring should furnish ligands more congruent with the structural requirements of σ_1 receptor binding. Additionally, it was anticipated that deviation from the core structure of regioisomers **2**–**4** might attenuate off-target interactions with the 5-HT_{2B} and D_2 receptors.

In order to produce analogs of **1** with improved σ_1 binding, we sought to elongate the alkyl chain represented by the dashed line in Figure 2, thereby extending the distance between the central piperazine and the phenyl ring. Utilizing **1** as a lead compound, 2-, 3-, and 4-methoxyphenyl analogs tethered to the piperazine nitrogen by a chain of 2, 3, or 4 methylene units were generated to explore the effect of linker elongation on σ receptor affinity and subtype selectivity.

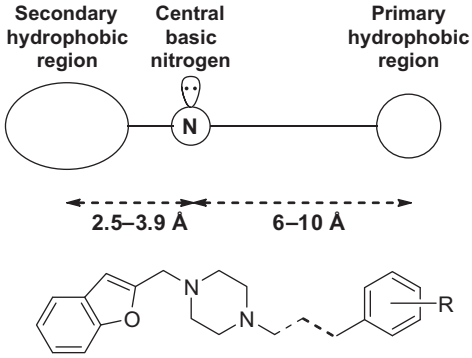


Figure 2. The Glennon σ_1 receptor pharmacophore and proposed orientation of binding for elongated *N*-(2-benzofuranylmethyl)-*N*′-arylalkylpiperazines.[37–39]

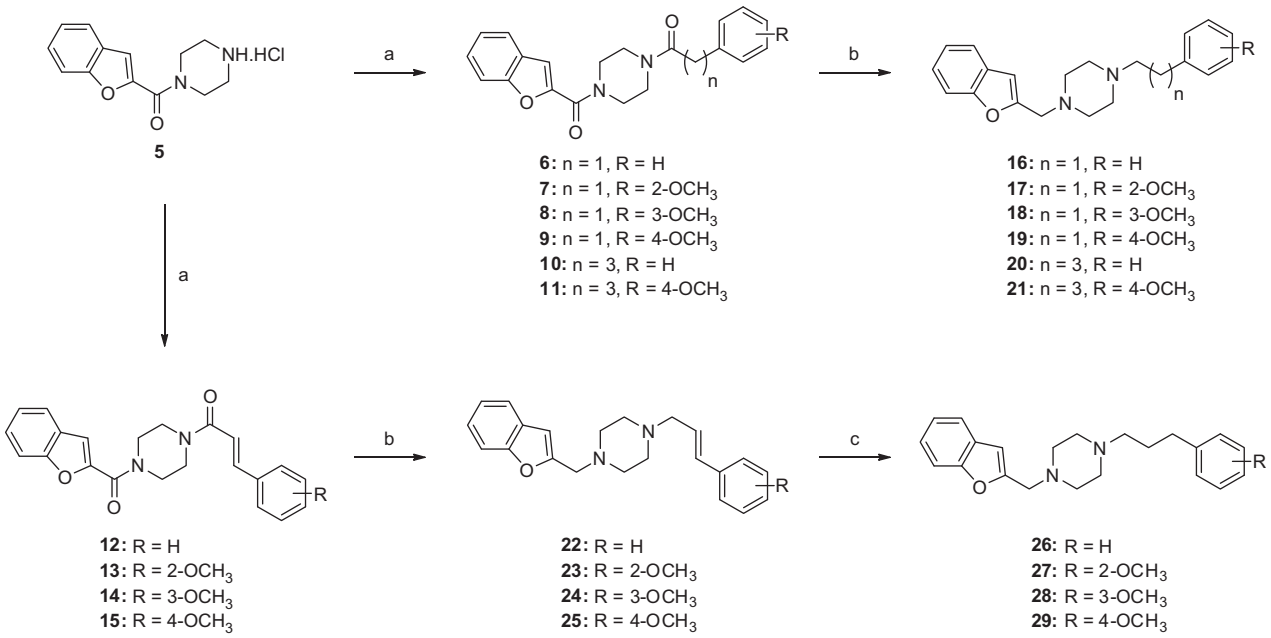
The desired piperazines were prepared according to the synthetic methods shown in Schemes 1 and 2. Benzofuranyl amine **5**, previously prepared in our laboratory,[35] was subjected to an amide coupling with the appropriate carboxylic acid in the presence of EDC and HOBt to furnish phenylacetamides (**6**–**9**), phenylbutyramides (**10** and **11**), and (*E*)-cinnamamides (**12**–**15**). Treating bisamides **6**–**15** with lithium aluminum hydride reduced both amide functionalities to give the corresponding piperazines **16**–**25** in moderate yields. The (*E*)-cinnamylamines (**22**–**25**), underwent hydrogenation to give saturated piperazines **26**–**29** in good yields.

An alternative synthetic strategy was undertaken to synthesize the remaining arylbutylpiperazines **30** and **31** (Scheme 2). Iodoanisoles **32** and **33** were each subjected to Sonogashira cross-coupling with 3-butynol to give the corresponding arylalkynes **34** and **35**, followed by hydrogenation to yield 4-arylbutanols **36** and **37** in high yields. Appel bromination of alcohols **36** and **37** afforded their respective arylalkyl bromides **38** and **39**,[40] which were subjected to amination using the previously described *N*-(2-benzofuranylmethyl)piperazine,[35] giving the desired phenylbutylpiperazines **30** and **31**.

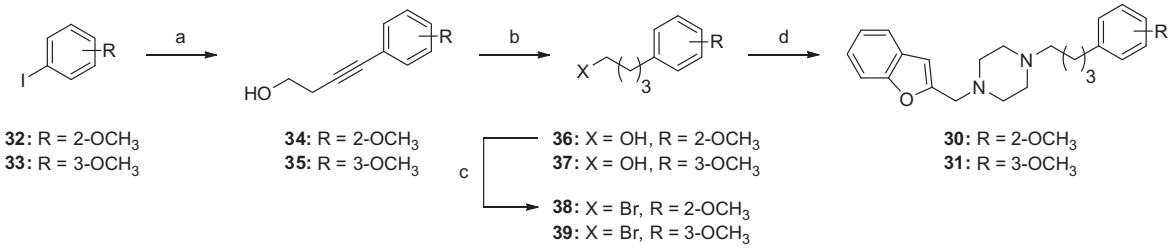
Binding affinities for newly synthesized compounds **16**–**21** and **26**–**31** at σ_1 and σ_2 receptors were determined from in vitro competition assays, using a modification of the protocol reported by Kovacs and Larson,[41] and are summarized in Table 1. Competitive displacement of [^{3}H](+)-pentazocine in a rat brain homogenate preparation was used to determine σ_1 receptor affinities, while competitive displacement of [^{3}H]DTG from a PC12 cell preparation provided σ_2 receptor affinities. K_i determinations and extensive CNS binding profiles were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program (NIMH PDSP).

Like parent compound **1**, most analogs within this series showed a distinct preference for the σ_1 receptor. Extending the length of the alkyl tether of **1**–**4** by a single carbon gave the corresponding phenethyl analogs **16**–**19**, which retained the high σ_1 receptor affinities (σ_1 K_i = 7.3–17 nM), generally observed for the benzylic series (excepting **2**). When compared to 2-methoxybenzyl derivative **2** (σ_1 K_i = 198 nM), 2-methoxyphenethyl **17** possessed affinity for σ_1 that was more than an order of magnitude greater (K_i = 17 nM), resulting in a compound that was selective for σ_1 rather than σ_2. The 3-methoxyphenethyl derivative **18** showed comparable σ_1 affinity to the corresponding benzylic analog **3**, but an increased σ_2 affinity, resulting in a lack of subtype selectivity overall (σ_1 K_i = 13 nM, σ_2 K_i = 14 nM). A 4-methoxy substitution pattern within the phenethyl series (**19**) conferred no advantage to σ_2 binding over the same substitution in the benzyl series (**4**), and reduced σ_1 affinity, to give a less σ_1-selective ligand (σ_1 K_i = 9.4 nM, σ_2/σ_1 = 11). Much like their benzylic analogs, the most σ_1-selective members of the phenethyl series were the simple phenethyl derivative **16** (σ_1 K_i = 7.3 nM, σ_2/σ_1 = 18) and the 4-methoxy-substituted **19** (σ_1 K_i = 9.4 nM, σ_2/σ_1 = 11), although levels of σ_1 selectivity for both compounds were lower than the corresponding benzyl derivatives.

Phenylpropyl analogs **26**–**29** retained high affinity for the σ_1 receptor (σ_1 K_i = 3.1–8.3 nM), comparable to those of the corresponding phenethyl derivatives (σ_1 K_i = 7.3–17 nM), along with moderate to high σ_2 affinities (σ_2 K_i = 18–138 nM). Consequently, **26**–**29** generally possessed poor σ_1 selectivity, with the notable exception of 4-methoxy substituted **29** (σ_1 K_i = 3.1 nM, σ_2/σ_1 = 45). The binding profile of **29** closely resembled that of the corresponding benzylic derivative **4**, making it one of the most selective σ_1 ligands identified within this series. Moreover, **29** showed substantially reduced off-target affinity (5-HT_{2B} K_i = 155 nM, D_2 K_i >10,000 nM) when compared to **4** (5-HT_{2B} K_i = 15 nM, D_2 K_i >2700 nM).

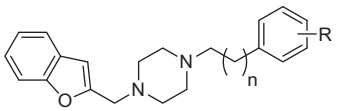


Scheme 1. Reagents and conditions: (a) $RPh(CH_2)_nCOOH$ or RPhCH=CHCOOH, NMM, EDC·HCl, HOBt, DMF, rt, 20 h, 61–88%; (b) $LiAlH_4$, Et_2O, 0 °C to reflux, 16 h, 61–82%; (c) H_2, HCl, 10% w/w Pd/C, MeOH, rt, 20 h, 78–82%.



Scheme 2. Reagents and conditions: (a) 3-butynol, $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (5 mol %), Et_3N, reflux, 20 h, **34**: 60%, **35**: quant.; (b) H_2, 10% w/w Pd/C, MeOH, rt, 20 h, **36**: quant., **37**: 88%; (c) CBr_4, PPh_3, Et_2O, rt, 16 h, **38**: 75%, **39**: quant.; (d) *N*-(2-benzofuranylmethyl)piperazine, K_2CO_3, NaI, DMF, reflux, 20 h, **30**: 72%, **31**: 74%.

Table 1
In vitro binding data for *N*-(2-benzofuranylmethyl)-*N′*-(methoxyphenylalkyl)piperazine derivatives **16**–**21** and **26**–**31**



Cmpd	*n*	R	K_i ± SEM[a] (nM)					
			5-HT_{2B}	D_2	NMDA/PCP	σ_1	σ_2	σ_2/σ_1
16	1	H	310 ± 18	NA	NA	7.3 ± 0.4	131 ± 10	18
17	1	2-OCH_3	120 ± 6	1648 ± 130	NA	17 ± 1	81 ± 4	5
18	1	3-OCH_3	290 ± 16	NA	NA	13 ± 1	14 ± 1	1
19	1	4-OCH_3	463 ± 29	NA	NA	9.4 ± 0.5	101 ± 9	11
26	2	H	147 ± 9	1025 ± 87	NA	5.7 ± 0.3	18 ± 2	3
27	2	2-OCH_3	628 ± 31	5866 ± 920	NA	8.3 ± 0.6	53 ± 7	6
28	2	3-OCH_3	243 ± 12	556 ± 54	NA	5.7 ± 0.4	40 ± 5	7
29	2	4-OCH_3	155 ± 7	NA	NA	3.1 ± 0.2	138 ± 13	45
20	3	H	275 ± 27	89 ± 10	NA	4.2 ± 0.3	18 ± 2	4
30	3	2-OCH_3	332 ± 26	432 ± 41	NA	16 ± 1	130 ± 15	8
31	3	3-OCH_3	343 ± 13	484 ± 47	NA	7.6 ± 0.7	211 ± 25	28
21	3	4-OCH_3	352 ± 21	5791 ± 921	NA	13 ± 1	87 ± 8	7

[a] Affinities for σ_1 were determined in rat brain homogenates using [^{3}H](+)-pentazocine, and for σ_2 in PC12 cells using [^{3}H]DTG. The values in this table represent the mean ± SEM from triplicate assays. NA = less than 50% inhibition at primary assay concentration (10 μM).

Compounds **20**, **21**, **30**, and **31**, featuring a four-carbon linker, displayed high σ_1 affinities (σ_1 K_i = 4.2–16 nM), with a simple phenylbutyl group conferring the greatest σ_1 affinity (20, σ_1 K_i = 4.2 nM). Although **20** showed good σ_1 affinity, it also possessed high affinity for σ_2 receptors (σ_2 K_i = 18 nM), with a net binding profile akin to the subtype nonselective phenylpropyl analog **26**, and contrasting the high σ_1 selectivity of the corresponding benzyl (**1**) and phenethyl (**16**) congeners. In stark contrast to **4** and **29**, a 4-methyl ether did not confer high σ_1 selectivity within the phenylbutyl series, and compound **21** (σ_1 K_i = 13 nM, σ_2/σ_1 = 7) showed a binding profile similar to that of the corresponding phenethyl analog **19** (σ_1 K_i = 9.4 nM, σ_2/σ_1 = 11). However, 3-methoxyphenylbutyl derivative **31** showed reasonable σ_1 selectivity (σ_1 K_i = 7.6 nM, σ_2/σ_1 = 28), unlike the 3-methoxy substituted members of the previous series (**3**, **18**, and **28**).

Excepting butyl analog **21**, derivatives comprising a methoxy group at the 4-position of the distal phenyl ring appear to be well tolerated at the σ_1 site, a trend similarly observed in our previous work.[35] The 4-methoxy-substituted derivative containing a propyl linker (**29**) showed the highest σ_1 affinity and selectivity (K_i = 3.1 nM, σ_2/σ_1 = 45) in this series of piperazines, comparable to compound **1**. It is postulated that a propyl linker between the central piperazine ring and flanking benzyl group is of a suitable distance for the aryl ring to accommodate the primary hydrophobic region of the σ_1 pharmacophore. In terms of off-target affinity, comparison of the 4-methyl ethers **4** and **29** showed that compound **29** possessed a 10-fold reduction in binding at the serotonin 5-HT_{2B} receptor, and negligible affinity (K_i >10 μM) for the D_2 dopamine receptor, relative to **4**.

The range of σ_2 affinities of **16**–**21** and **26**–**31** were more widely varied than those of **1**–**4** at the same site. Although the 3-methoxyphenethyl analog showed the greatest σ_2 affinity (**18**, σ_2 K_i = 14 nM), the next most prominent σ_2 interactions were demonstrated by the simple phenylpropyl and phenylbutyl derivatives (**26** and **20**, respectively), with each possessing a σ_2 K_i value of 18 nM. Within the current series it appears that methoxy-subsitution of the phenyl ring is not inherently required for high σ_1/σ_2 affinity, and may be generally detrimental to σ_2 binding. A conclusive σ_2 receptor pharmacophore has not yet been proposed, although optimal structural features are believed to resemble those for σ_1 binding, thereby accounting for the myriad of high affinity σ_2 ligands displaying less than 10 times subtype selectivity—including **18**, **20**, and **26**.[42]

Considered together, the σ_1 affinities and subtype selectivities of piperazines **16**–**21** and **26**–**31** (K_i = 3.1–17 nM) were comparable to benzylic analogs **1**, **3**, and **4** (K_i = 2.7–16 nM). Moreover, the affinities of **16**–**21** and **26**–**31** for the 5-HT_{2B} receptor (K_i = 120–628 nM) were similar to σ_1-selective **1** (K_i = 497 nM); much lower than the relatively nonselective methoxybenzylic analogs **2**–**4** (K_i = 9.7–28 nM). However, several ligands from the present work showed increased off-target interaction with D_2 dopamine receptors compared to the micromolar affinities of **1**–**4** at the same site, most notably **20**, **28**, **30**, and **31** (K_i = 89–556 nM).

We have developed a series of subtype selective σ receptor ligands by amalgamating lead structure **1** with the σ_1 pharmacophore proposed by Glennon et al.[37–39] The σ receptor affinities of these linker-elongated arylalkylpiperazines revealed that 4-methoxyphenyl groups are generally well tolerated at σ_1, with subtype selectivities comparable to that of **1**. Within this series, the 4-methoxy-substituted phenylpropylpiperazine **29** was identified as a high-affinity σ_1 receptor ligand (K_i = 3.1 nM, σ_2/σ_1 = 45), with lower affinity for other CNS receptors. The binding profile of compound **29** suggests that it may be suitable for the development of a carbon-11-labeled tracer for imaging σ_1 receptors using positron emission tomography (PET).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.08.029.

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