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PHENYTOIN DERIVATIVES AS POTENT σ LIGANDS

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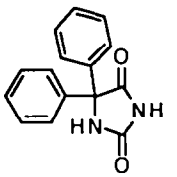
Abstract: A series of 4-phenylpiperidinyl and 4-phenylpiperazinyl alkyl spaced 5,5-diphenylhydantoins was prepared and evaluated for affinity at σ sites. Increasing the alkyl spacer between the two pharmacophore recognition units resulted in a progressive increase in σ binding affinity. The pentyl **12** and hexyl **13** 4-phenylpiperdine derivatives exhibited subnanomolar affinity (0.7 nM and 0.6 nM) for the PENT site.

The σ recognition site was originally identified as a novel binding site in brain with high affinity for (+)benzomorphans and certain antipsychotics.[2] As a result of this information the σ site has been hypothesized to play a role in psychosis[3] and σ ligands have been proposed as potential antipsychotic agents which may lack the extrapyramidal side effects or tardive dyskinesia associated with convential antipsychotic therapy.[4] Recently, antiischemic and neuroprotective effects have been reported among structurally diverse classes of σ ligands, and a link between σ and N-methyl-D-aspartate (NMDA) receptors has been proposed to account for some of the neuroprotective effects observed.[5]



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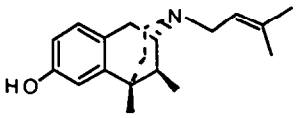

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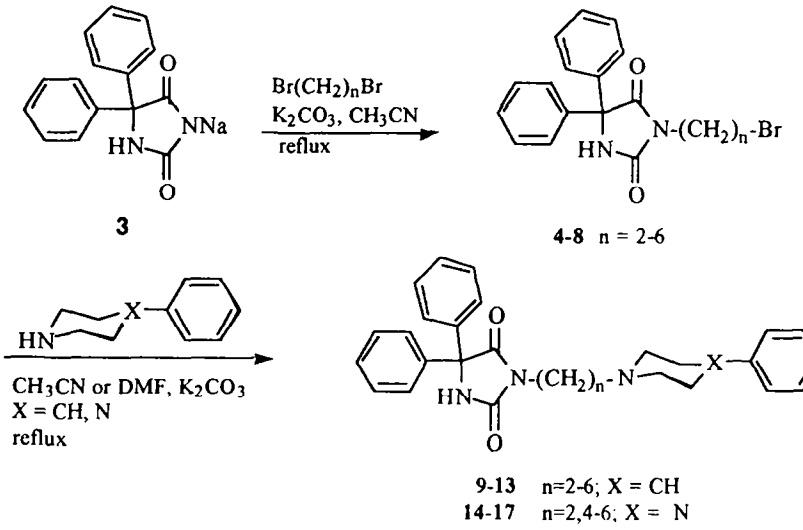
The anticonvulsant 5,5-diphenylhydantoin **1** (phenytoin) is an important tool for the study of σ binding. We have recently demonstrated phenytoin can allosterically modulate binding of σ ligands to the [^{3}H](+)pentazocine (**2**) labeled site,[6] implying that phenytoin may bind to a distinct site near the competitive ligand site. The 4-phenylpiperidine moiety is a proposed pharmacophore for binding to the competitive σ site.[2,7] Combining these pharmacophores led to the design of a series of 4-phenylpiperidinyl alkyl-spaced 5,5-diphenylhydantoins. The compounds were synthesized and evaluated for affinity at σ_1 and σ_2 sites using [^{3}H](+)pentazocine (PENT) and [^{3}H]1,3-di(2-tolyl)guanidine (DTG) as ligands. The rationale for the design of this series was to probe the spatial relationship of the allosteric or lipophilic phenytoin site with the competitive σ binding site.

Chemistry

The compounds were synthesized as shown in Scheme 1. The 3-(bromoalkyl)-5,5-diphenylhydantoins were prepared by a modification of the procedure to prepare the known 3-(2-bromoethyl)-5,5-diphenylhydantoin **4** and 3-(3-bromopropyl)-5,5-diphenylhydantoin[8] **5** by reaction of sodium 5,5-diphenylhydantoin **3** with an excess of the appropriate dibromoalkane (CH_3CN, anhydrous K_2CO_3) to give the mono-alkylated bromohydantoins **4-8** in 82-88% yield. Alkylation of 4-phenylpiperidine with the bromo derivatives **4-8** gave the desired C_2-C_6 alkyl-spaced piperidinyl-hydantoin derivatives **9-13** in good yield.[9] Similarly, alkylation of 1-phenylpiperazine with **4** and **6-8** readily gave the C_2 and C_4-C_6 alkyl-spaced piperazine derivatives **14-17**.[9]

Scheme 1

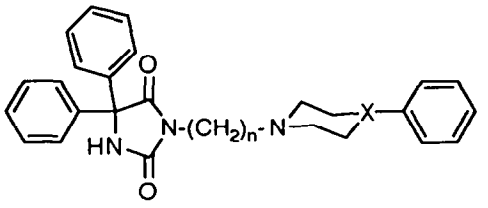


Results and Discussion

An examination of the data in table 1 reveals σ binding affinity increases directly with increasing alkyl distance between the 5,5-diphenylhydantoin and the 4-phenylpiperidine pharmacophore. The 2- and 3-carbon spaced piperidinyl derivatives **9** and **10** showed moderate affinity for both the PENT- (17 and 22 nM) and DTG- (43 and 25 nM) defined σ sites. The butyl derivative **11** showed a 2-fold increase in affinity for the PENT site and a 3-fold increase for the DTG-labeled site compared to **10** Increasing the distance between these two key features to 5 and 6 carbons showed a further enhancement in affinity for both σ sites and resulted in potent σ ligands. The pentyl **12** and hexyl **13** derivatives exhibited subnanomolar affinity (0.7 nM and 0.6 nM) for the site labeled by PENT, and 4 5 nM and 3 0 nM for the DTG-defined σ site. Due to decreased water solubility the alkyl linker distance was not further increased To further explore the σ binding affinity of this series the 4-phenylpiperazines **14-17** were also synthesized and evaluated The piperazine derivatives were less potent than the corresponding piperidines Important was the fact that the

binding affinity of the piperazines also improved with increasing alkyl spacer length, indicating that the piperidines and piperazines share a common mode of interaction with the binding site.

Table 1. σ Binding Affinities of Bivalent Diphenylhydantoin Analogs.



Compound	n	X	mp (%)	Anal.	σ Binding K_i, nM [^{3}H](+)PENT	[^{3}H]DTG
9	2	CH	175-178 (45)	FB	17 ± 4	43 ± 11
10	3	CH	166-168 (52)	FB	22 ± 4	25 ± 1
11	4	CH	217-218 (74)	HCl	10 ± 2	8.4 ± 1.4
12	5	CH	166-167 (66)	FB	0.7 ± 0.2	4.5 ± 0.8
13	6	CH	231-233 (65)	HCl	0.59 ± 0.06	3.0 ± 0.4
14	2	N	175-180 (42)	HCl	664 ± 101	842 ± 85
15	4	N	108-109 (62)	FB	328 ± 65	49 ± 8
16	5	N	145-146 (55)	FB	19 ± 2	19 ± 2
17	6	N	120-122 (61)	HCl	13 ± 4	11 ± 2
(+)Pentazocine **2**					2.1 ± 0.1	562 ± 165
Haloperidol					0.6 ± 0.1	6.0 ± 0.6
BMY-14802					265 ± 46	164 ± 42
DTG					107 ± 21	70 ± 11

Data are the mean ± SEM of at least three separate determinations performed in triplicate. Ligand conc. was 0.5 nM for (+)PENT and 4 nM for DTG binding in guinea pig brain homogenates. Binding was performed as described previously.[10] Anal. for CHN; FB = free base, HCl analysis of the HCl salt.

The three primary recognition sites on the σ binding site are a primary lipophilic site and a site capable of binding a nitrogen atom, and a second lipophilic site which can be utilized in ligand binding.[10,11] The 4-phenylpiperidine moiety, which is found in the (+)benzomorphan skeleton and in the potent σ ligand haloperidol, has been proposed to be the primary σ site pharmacophore.[2,7,10] Importantly, proper occupation of the second lipophilic site has been reported to significantly enhance σ binding affinity.[10] The results of these data indicate the σ receptor is capable of accommodating the bulky 5,5-diphenylhydantoin lipophilic moiety. Hill values for the novel ligands were near unity, indicating a competitive interaction.

We have utilized an approach similar to the bivalent ligand approach to design novel σ ligands. Bivalent ligands are defined as molecules that contain two receptor recognition units linked through a spacer.[12] An assumption of this approach is that enhanced potency and selectivity can be achieved by simultaneous occupation of proximal recognition sites by both groups of the bivalent ligand. The effectiveness with which the two pharmacophore units in the 4-phenylpiperidinyl-diphenylhydantoins bridge their respective recognition sites depends on the length of the alkyl spacer. Subnanomolar affinity for the PENT site was achieved with a spacer of five or six methylenes, whereas weaker affinity was found with the derivatives with shorter spacers. These compounds are potent σ ligands and further biological evaluation is in progress.

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