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Molecular hybridization of 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$] dodecane-3-ol with sigma (σ) receptor ligands modulates off-target activity and subtype selectivity

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ABSTRACT

A series of N-substituted 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ols incorporating the respective arylalkyl subunits from several known sigma (σ) receptor ligands were synthesized and evaluated for their affinity against σ receptors and dopamine receptors. The hybrid trishomocubane-derived ligands (**4**–**6**) showed good selectivity for σ_1 and σ_2 receptors over multiple dopamine receptors. The molecular hybrid obtained from haloperidol and 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ol (**4**, σ_1 K_i = 27 nM, σ_2 K_i = 55 nM) showed reduced affinity for D_1–D_5 dopamine receptors when compared to haloperidol itself. The compound with the greatest σ_1 affinity in the series, benzamide **4** (σ_1 K_i = 7.6 nM, σ_2 K_i = 225 nM) showed a complete reversal of the subtype selectivity displayed by the highly σ_2 selective parent benzamide, RHM-2 (**3**, σ_1 K_i = 10412 nM, σ_2 K_i = 13.3 nM).

Since their discovery 35 years ago, sigma (σ) receptors continue to be widely studied.[1,2] Two σ receptor subtypes have been well defined pharmacologically, σ_1 and σ_2, differing in size, distribution, and drug selectivity.[3] The σ_1 receptor has been cloned from numerous mammalian tissue sources, including human brain, and shares no homology with any known mammalian protein.[4] σ_1 receptors are primarily located at the interface between endoplasmic reticulum (ER) and mitochondria, the mitochondria-associated ER membrane (MAM), where they control cellular Ca^{2+} levels by acting as molecular chaperones for type 3 inositol 1,4,5-triphosphate IP_3 receptors.[5] However, σ_1 receptors can also translocate to the plasma membrane where they modulate K^+ and Cl^- channels.[6,7] Additionally, σ_1 receptors have been shown to regulate the neurotransmission mediated by acetylcholine,[8] dopamine,[9] glutamate,[10] 5-hydroxytryptamine (5-HT),[11] and norepinephrine,[12] accounting for their diverse pharmacology.

The σ_2 receptor is yet to be cloned, and much less is known about its molecular structure and biochemical function. It was recently proposed that the σ_2 receptor may belong to the histone protein family.[13] Like σ_1 receptors, the primary role of σ_2 receptors is thought to involve Ca^{2+} modulation, although the precise signal transduction pathways remain unclear.[14] The over-expression of σ_2 receptors in several tumor cell lines,[15,16] has led to the proposal of σ_2 receptors as therapeutically useful biomarkers for the noninvasive assessment of tumor proliferation using positron emission tomography (PET),[17,18] and several potential PET agents have been described.[19] Moreover, σ_2 receptors have shown promise as a target for the treatment of drug-resistant cancers.[20,21]

Despite the current shortcomings in our understanding of σ receptors, much is known about their links to disease.[22,23] Indeed, σ receptors have been implicated in the pathophysiology of a diverse spectrum of central nervous system (CNS) diseases, including anxiety disorders,[24] depression,[25,26] psychotic disorders,[27] Alzheimer's disease,[28] and drug addiction.[29] Many clinically-utilized antidepressant and antipsychotic drugs,[30–32] as well as drugs of abuse,[33] have been shown to act at σ_1/σ_2 receptors at physiologically relevant concentrations. Although σ receptors represent promising targets for the development of novel treatments for several CNS diseases, the elucidation of the function and structure of σ_1 and σ_2 receptors has been hampered by the historical lack of truly selective ligands.

Many early σ receptor ligands, such as the clinical antipsychotic haloperidol (**1**, Fig. 1), showed little σ selectivity. Haloperidol is a classic 'dirty drug', possessing high affinity for σ_1 (reported K_i values range from 0.90 to 10 nM)[34–36] and σ_2 (reported K_i values range from 7.93 to 78 nM) receptors[34–36] in addition to many other CNS sites, particularly dopamine, 5-HT, α adrenergic, and histamine receptors.[37–40] Several selective σ_1 receptor ligands have now been reported, including NE-100 (**2**).[41] NE-100 shows high affinity for the σ_1 receptor subtype, comparable to that of haloperidol, but approximately 205-fold selectivity over the σ_2 receptor

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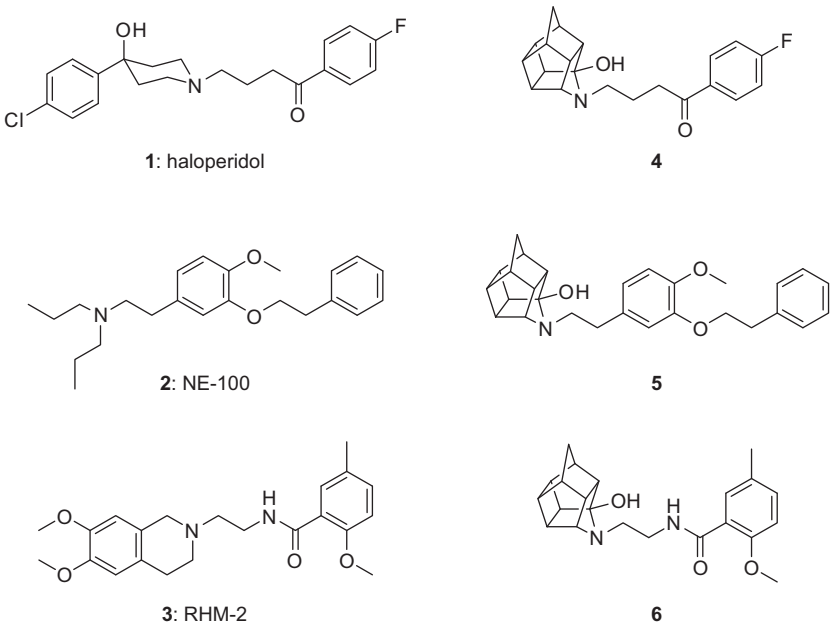


Figure 1. Known σ ligands and their corresponding 'hybrid' 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ol analogs.

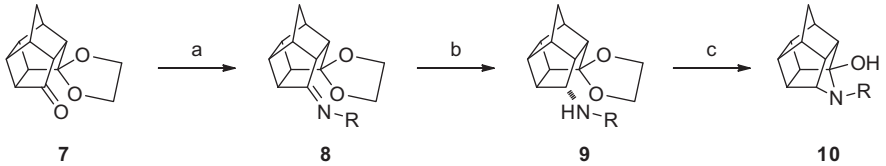
(σ_1 K_i = 1.03 nM, σ_2 K_i = 212 nM).[42] Unlike haloperidol, NE-100 is a selective σ ligand, displaying negligible affinity at other CNS sites.[41] Fewer selective σ_2 receptor ligands are known, however Mach and co-workers have reported the σ_2 selectivity of several benzamides, such as RHM-2 (**3**).[43,44] RHM-2 shows high affinity and selectivity for the σ_2 receptor subtype (K_i = 13.3 nM, σ_1/σ_2 = 783), with only micromolar affinity for D_2 and D_3 dopamine receptors.[43,44]

We recently reported structure-affinity relationships for a small series of N-substituted 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ols with affinity for σ_1/σ_2 receptors, and selectivity over other CNS receptors, transporters, and ion channels.[45] These polycarbocyclic hemiaminals demonstrate promising pharmacological activity, both in vitro[46] and in vivo.[47] To further explore the σ selectivity conferred by this polycarbocyclic hemiaminal scaffold, we sought to synthesize chimeric structures incorporating the arylalkyl subunits from known σ ligands. Compounds **1**–**3** were selected as candidate parent molecules based on the diversity of their binding profiles, and are shown in Figure 1 alongside the proposed, molecular-hybrid N-substituted 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ols (**4**–**6**, respectively). Haloperidol, with its dual σ_1/σ_2 binding profile and significant dopaminergic activity, was included to determine whether incorporation of the 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ol moiety could improve selectivity for σ receptors over dopamine receptors. Compounds **2** and **3** were chosen to determine the effect of 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ol incorporation on their selectivity for σ_1 and σ_2 receptors, respectively. Additionally, **1**–**3** each contain only a single basic nitrogen atom, limiting the possibility of multiple binding modes for **4**–**6**.

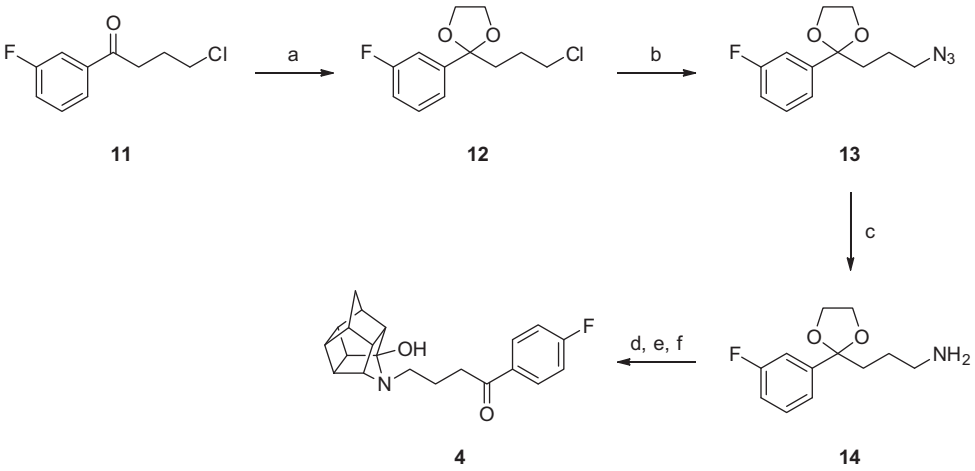
The synthetic route to N-substituted 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ols (**10**, Scheme 1)[45] involves the condensation of Cookson's diketone monoethylene acetal (**7**) with the desired primary amine under pressure, and subsequent reduction of formed imine **8** using sodium borohydride, gives endo-amine **9**. Hydrolysis of ketal **9** by aqueous hydrochloric acid in acetone, followed by a basic work-up, gives transannularly-cyclized hemiaminals of type **10** in reasonable yield over three steps. This general route was amenable to the production of **4**–**6**, but required the synthesis of the necessary primary amine reactants.

The synthesis of haloperidol analog **4** is shown in Scheme 2. 4-Chloro-4′-fluorobutyrophenone (**11**) was treated with ethylene glycol in the presence of catalytic *p*-toluenesulfonic acid under Dean–Stark conditions to give acetal **12**. Nucleophilic substitution of the chloro group to give azide **13** was achieved under relatively mild conditions by using a stoichiometric amount of potassium iodide. Staudinger reduction of the azide afforded primary amine **14**. Subjecting **14** to the conditions outlined in Scheme 1 gave **4** in 42% yield over three steps.

The synthesis of NE-100 analog **5** (Scheme 3) started with phenethyl bromide alkylation of isovanillin (**15**) to afford aldehyde **16**. Subjecting **16** to a Henry reaction under classical conditions gave nitrostyrene **17**. Complete reduction of the α,β-unsaturated nitro group of **17** was achieved using lithium aluminium hydride, to give desired amine **18**. Subjecting **18** to the conditions described in Scheme 1 gave **5** in 50% yield over three steps. Alternatively, reductive alkylation of **18** with propanal using sodium triacetoxyborohydride gave NE-100 in excellent isolated yield. This novel route to NE-100 proceeds in 56% unoptimized yield over four steps and rep-



Scheme 1. Reagents and conditions: (a) R–NH_2, EtOH, 100 °C, 18 h; (b) $NaBH_4$, EtOH, rt, 8 h; (c) aq 4 M HCl, acetone, rt, 12 h, basic work-up.



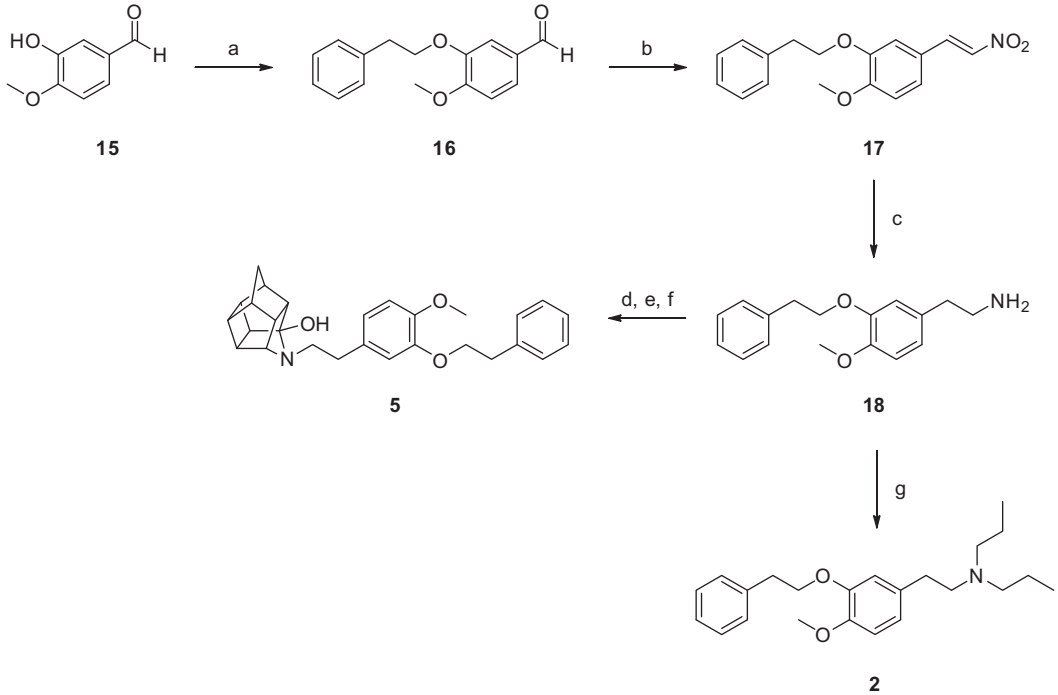
Scheme 2. Reagents and conditions: (a) $HOCH_2CH_2OH$, *p*-TsOH (cat.), PhMe, reflux, Dean–Stark conditions, 16 h, 98%; (b) NaN_3, KI, DMF, 60 °C, 26 h, 96%; (c) PPh_3, Et_2O, 0 °C to rt, then H_2O, 22 h, 95%; (d) **7**, EtOH, 100 °C, 18 h; (e) $NaBH_4$, rt, 8 h; (f) aq 4 M HCl, acetone, rt, 12 h, 42% over three steps.

resents a synthetically expedient improvement over the previously reported sequence of eight steps.[48]

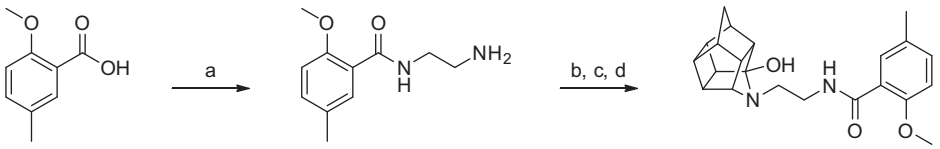
The synthesis of RHM-2 analog **6** is shown in Scheme 4. Commercially available 2-methoxy-5-benzoic acid (**19**) was activated with carbonyldiimidazole (CDI) and treated with an excess of 1,2-diaminoethane, easily removed during aqueous work-up, to give amide **20**. Subjecting **20** to the conditions described in Scheme 1 gave **6** in 65% yield.

The hemiaminals thus synthesized (**4**–**6**) were subjected to binding assays against a panel of CNS receptors (see Table S1 for full binding profiles). The K_i values for **4**–**6** at σ_1 and σ_2 receptors, and D_1–D_5 dopamine receptor subtypes are shown in Table 1. Rat brain homogenates were used as the source of σ_1 receptors, whilst PC12 cells were used as the σ_2 receptor source. All dopamine receptor assays employed transfected human embryonic kidney cells expressing the human forms of dopamine receptor subtypes. The radioligands [^{3}H](+)-pentazocine and [^{3}H]DTG were used in the σ_1 and σ_2 receptor assays, respectively, whilst [^{3}H] SCH233930 and [^{3}H]*N*-methylspiperone were employed in the D_1 and D_5, and D_2–D_4 assays, respectively.

The hybrid analogs **4**–**6** were all moderately selective for the σ_1 receptor. In the case of haloperidol analog **4**, the mixed σ_1/σ_2 binding profile of haloperidol itself was retained. The σ_1 and σ_2 K_i values for **4** (27 and 55 nM, respectively) reveal comparable σ_2 binding, but reduced σ_1 binding, when compared to its parent structure **1**. The off-target activity of **4** was diminished at all dopamine receptor subtypes screened (D_1–D_5) relative to haloperidol. At D_1 and D_4 receptors, **4** (D_1 K_i = 209 nM, D_4 K_i = 93 nM) demonstrated less than a 10-times and 20-times reduction in binding affinity, respectively, when compared to **1** (D_1 K_i = 25 nM,[40] D_4



Scheme 3. Reagents and conditions: (a) $PhCH_2CH_2Br$, K_2CO_3, DMF, 50 °C, 19 h, 90%; (b) CH_3NO_2, NH_4OAc (cat.), AcOH, reflux, 4 h, 95%; (c) $LiAlH_4$, Et_2O/THF (80:20), reflux, 42 h, 68%; (d) **7**, EtOH, 100 °C, 18 h; (e) $NaBH_4$, rt, 8 h; (f) aq 4 M HCl, acetone, rt, 12 h, 50% over three steps; (g) CH_3CH_2CHO, $NaBH(OAc)_3$, rt 18 h, 96%.



19 20 6

Scheme 4. Reagents and conditions: (a) CDI, THF, rt, 1 h, then $H_2NCH_2CH_2NH_2$ (20 equiv), 19 h, 95%; (b) **7**, EtOH, 100 °C, 18 h; (c) $NaBH_4$, rt, 8 h; (d) aq 4 M HCl, acetone, rt, 12 h, 65% over three steps.

Table 1
Binding affinities of compounds **4**–**6** for σ receptors (σ_1 and σ_2) and dopamine receptors (D_1–D_5)

Compound	K_i (nM ± SEM)[a]						
	σ_1	σ_2	D_1	D_2	D_3	D_4	D_5
4	27 ± 2	55 ± 4	209 ± 36	1724 ± 316	1958 ± 146	93 ± 8	>10000
5	20 ± 1	93 ± 5	>10000	>10000	ND	ND	ND
6	7.6 ± 1.0	225 ± 18	ND	>10000	>10000	ND	ND
Haloperidol (**1**)[b]	0.90–10	7.93–78	25	1	29	5	48
NE-100 (**2**)[c]	1.03	212	>10000[e]	>10000[e]	ND	ND	ND
RHM-2 (**3**)[d]	10412	13.3	ND	2850	3760	ND	ND

ND = not determined.
[a] K_i values represent the mean ± SEM of four experiments.
[b] Data extracted from Refs. 34–40.
[c] Data extracted from Refs. 41–42.
[d] Data extracted from Refs. 43–44.
[e] IC_{50} (nM ± SEM).

K_i = 5 nM).[37] However, the reduction in binding of **4** at D_3 and D_5 receptors (D_3 K_i = 1958 nM, D_5 K_i >10 μM) compared to haloperidol was more significant, approximately 67-times and more than 200-times, respectively. Most notable was the diminished binding of **4** at D_2 receptors, a key pharmacological target for the activity of **1**, where a greater than 1700-fold reduction in binding was observed (D_2 K_i = 1724 nM).

NE-100 analog **5** displayed moderate σ_1 affinity (K_i = 20 nM), and modest subtype selectivity (σ_2/σ_1 = 4.7). Compared to NE-100 itself, **5** showed a decrease in σ_1 affinity, and higher levels of σ_2 binding, leading to a compound of low σ_1 selectivity. NE-100 itself displays no significant off-target activity,[41] and this σ selectivity was retained by molecular hybrid **5**.

Benzamide **6** showed the highest σ_1 affinity (K_i = 7.6 nM) within this series of analogs, and only moderate affinity for σ_2 receptors (K_i = 225 nM). The selectivity of **6** for σ_1 over σ_2 receptors, albeit modest (~30-fold), represents a profound reversal of the high σ_2 selectivity—more than 780-fold over σ_1 sites—demonstrated by the parent compound RHM-2.[43,44] Additionally, the micromolar affinity of the parent compound for D_2 and D_3 receptors was abolished in **6** (D_2 K_i >10 μM, D_3 K_i >10 μM).

Taken together, the binding profiles of **4**–**6** highlight the utility of the 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ol scaffold for the development of highly selective σ receptor ligands. In order to better understand and exploit the role of 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ol in conferring sigma receptor binding and selectivity, current investigations are focussed on the importance of the distance between the hemiaminal nitrogen and aryl group within this class of compounds, and will be presented in due course.

Acknowledgments

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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.2011.04.098.

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