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NOVEL SIGMA RECEPTOR LIGANDS 2.

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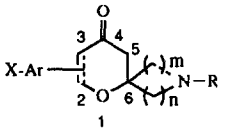
Abstract: The preparation and SAR of the series of substituted 2,3-dihydro-4H-pyran-4-one which demonstrate potent selective binding to the sigma ligand binding site are reported.

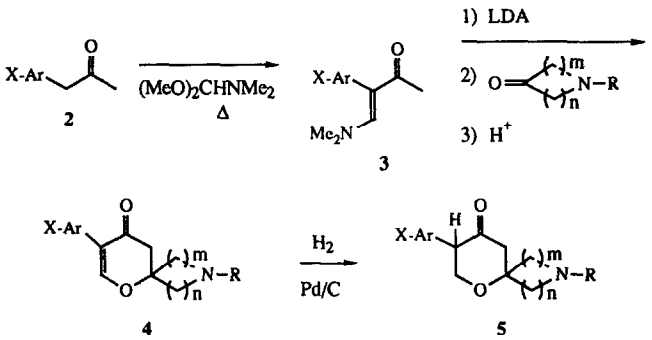
The accompanying communication described a novel class of potent, selective sigma receptor ligands.[2] This paper reports the preparation and SAR of a related class of sigma ligands. The general structure for these compounds is represented by **1**.



1

Structure **1** contains three fixed features: an aryl moiety, a basic nitrogen and a 2,3-dihydro-4H-pyran-4-one. Features varied in order to evaluate structure activity relationships were substituents on the aryl ring (X), the molecular architecture connecting the pyranone and the basic nitrogen (m,n), the aryl group (Ar), nitrogen substituents (R), and pyranone substitution pattern. These compounds were readily prepared via the synthesis delineated in Schemes 1 and 2.[3]

Scheme 1

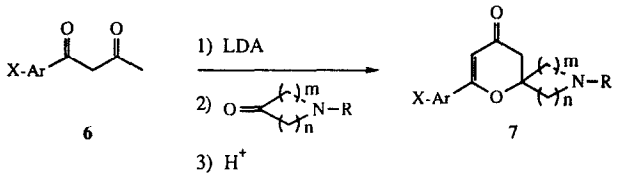


The route outlined in Scheme 1 utilized chemistry developed by Vinick and Gschwend.[4] Condensation of aryl acetone **2** (X=4-F) with DMF dimethylacetal yielded vinylgous amine **3** (63%). Treatment of **3** with LDA in THF at -78°C for 1 hr followed addition of appropriately substituted ketoamine yielded an adduct which was not isolated. Aqueous acidic workup (3 hr) led to the formation of desired cyclized product **4** (52%; m,n=2; X=4-F;

R=CH_2CH_2Ph). One example of reduced pyranone **5** (m,n=2; X=4-F; R=CH_2CH_2Ph) was prepared by hydrogenation of **4** over 10% palladium on carbon for 24 hr.

Pyranones with an alternative aryl substitution pattern were readily prepared by the route delineated in Scheme 2.

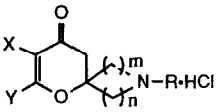
Scheme 2

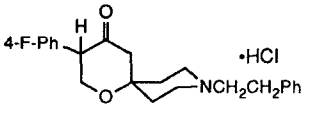


Treatment of diketone **6** (X=H) with two equivalents of LDA at -10°C for 1 hr followed by addition of ketoamine to dianion cooled to -78°C gave the adduct.[5] Aqueous acidic workup (24 hr) yielded cyclized adduct **7** (41%; m,n=2; X=H; R=CH_2CH_2Ph).

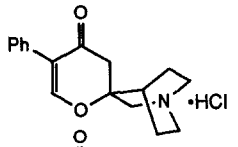
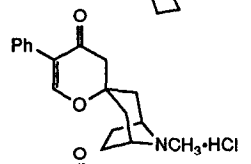
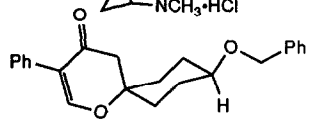
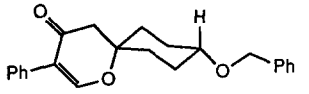
The compounds prepared for this study are listed in the following Table. The SAR data generated in the accompanying study on related furanones were used to guide target selection in this study. These compounds were evaluated for sigma receptor binding and dopamine (D_2) receptor binding activity according to the method of Tam and Cook[2,6] and for PCP receptor binding activity according to Vignon et al.[7] Sigma receptors were labeled by [^{3}H](+)-SKF 10,047. Dopamine D2 receptors and PCP receptors were labeled by [^{3}H]spiperone and [^{3}H]TCP, respectively. Each assay was run in duplicate.

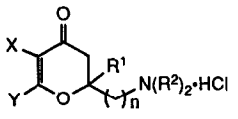
Comparative Binding Data for 2,3-dihydro-4H-pyran-4-one

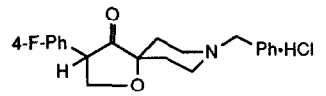


	X	Y	m	n	R	Binding Data (Ki nM) σ	D_2	PCP
8	Ph	H	2	2	Me	6880	$>10^5$	--
9	4-F-Ph	H	2	2	Me	7300	$>10^5$	--
10	Ph	H	2	2	CH_2Ph	4	1460	--
11	Ph	H	2	2	CH_2CH_2Ph	5	2030	$>10^4$
12		H	2	2	CH_2CH_2Ph	7	1080	--
13	2-F-Ph	H	2	2	CH_2CH_2Ph	1	2330	$3x10^4$
14	4-F-Ph	H	2	2	CH_2CH_2Ph	6	2900	1690
15	4-CH_3OPh	H	2	2	CH_2CH_2Ph	30	1496	--
16	Ph	H	3	1	CH_2Ph	13	--	--
17	4-F-Ph	H	3	1	CH_2Ph	131	8780	$>10^4$
18	H	Ph	2	2	CH_2CH_2Ph	10	4200	--
19	H		2	2	CH_2CH_2Ph	70	7600	--
20						4	1530	$1.4x10^4$

(Continued)

		σ	D_2	PCP
21		1590	$>10^4$	--
22		1830	$>10^4$	--
23		$>10^4$	$>10^4$	$>10^4$
24		7500	$>10^4$	$>10^4$



	X	Y	n	R^1	R^2			
25	Ph	H	1	CH_3	CH_3	352	4100	--
26	Ph	H	3	CH_3	CH_2CH_3	34	$>10^4$	$>10^4$
27						4	47	2230

The data presented in the Table suggest that in the 3- and 4-piperidone based derivatives, the N-benzyl and phenethyl analogs (**10-19**) consistently display potent sigma receptor binding and low affinity for D_2 and PCP receptors. Neither the nature of the aryl substituent nor its position on the pyranone ring appear to contribute significantly to the activity of these compounds. Clearly, N-methyl substituents (**8**,**9**,**22**) dramatically reduce sigma binding potency in the spiro cyclic analogs. Bicyclo analogs (**21**,**22**) demonstrate very modest activity, although the N-benzyl or phenethyl derivative of **22** might display greater potency than the N-methyl derivative **22**.

Saturation of the pyranone (**20**) has little effect on either the sigma receptor binding or receptor selectivity. The receptor selectivity was significantly eroded in the saturated furanone (**27**) reported in the accompanying article,[2] suggesting that subtle distinctions exist between the furanone and pyranone sigma receptor ligands.

A limited examination of non-spirocyclic analogs (**25**,**26**) suggests that a wide variety of open molecular architectures may possess selective sigma receptor binding. Resolution of compounds such as **16** or **26** would be useful in delineating the absolute stereochemical requirements of the sigma receptor.

Finally, the binding activity of two non-nitrogenous analogs (**23**,**24**) of the potent sigma ligand **14** is consistent with the requirement of a basic nitrogen for sigma receptor affinity.

The SAR data presented in this communication, like that reported in the preceding paper, are not consistent with the molecular model of the sigma receptor proposed by Manallack.[8] The lack of D_2 binding is consistent with the Olsen model.[9] The aryl π-N distance is 8.2Å for representative compound **14**, substantially outside the 5-7Å observed in most D_2 antagonists.[9,10]

Based on these preliminary data, several compounds, particularly **14**, were selected for additional preclinical evaluation. These results will be reported in due course.

References and Notes

1. Current address: American Cyanamid Company, Medical Research Division, Lederle Laboratories, Middletown Road, Pearl River, NY 10965.
2. Schow, S.R.; Tam, S.W. *Bioorg. Med. Chem. Lett.* and references cited therein.
3. All compounds were characterized by 90 MHz NMR spectra and low resolution mass spectral analysis; purity was demonstrated by TLC analysis. Salient data on the following examples: **1** **4** NMR($CDCl_3$) δ 2.69 (s,$COCH_2$), 7.44 (s,C=CHO-); m/e = 365 (M^+); **1** **8** NMR($CDCl_3$) δ 2 43 (s,$COCH_2$), 5 70 (s,COCH=C); m/e = 347 (M^+).
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10. Authors wish to acknowledge modeling studies performed by J. Krwyko (Du Pont) and R. Babine (Lederle).